Evidence Report/Technology Assessment

Number 217

Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update)

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • **www.ahrq.gov**

Evidence-Based Practice

Evidence Report/Technology Assessment
Number 217

Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update)

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2012-00006-I

Prepared by:
Southern California Evidence-based Practice Center
Santa Monica, CA

Investigators:
Sydne J. Newberry, Ph.D.
Mei Chung, Ph.D., M.P.H
Paul G. Shekelle, M.D., Ph.D.
Marika Suttorp Booth, M.S.
Jodi L. Liu, M.S.
Alicia Ruelaz Maher, M.D.
Aneesa Motala, B.A.
Mike Cui, M.P.H.
Tanja Perry, B.H.M.
Roberta Shanman, M.L.S.
Ethan M. Balk, M.D., M.P.H

AHRQ Publication No. 14-E004-EF
September 2014

This report is based on research conducted by the Southern California Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2012-00006-I). The findings and conclusions in this document are those of the author(s), who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This report may periodically be assessed for the urgency to update. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

This document is in the public domain and may be used and reprinted without permission except those copyrighted materials that are clearly noted in the document. Further reproduction of those copyrighted materials is prohibited without the specific permission of copyright holders.

Persons using assistive technology may not be able to fully access information in this report. For assistance, contact EffectiveHealthCare@ahrq.hhs.gov.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Newberry SJ, Chung M, Shekelle PG, Booth MS, Liu JL, Maher AR, Motala A, Cui M, Perry T, Shanman R, Balk EM. Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update). Evidence Report/Technology Assessment No. 217. (Prepared by the Southern California Evidence-based Practice Center under Contract No. 290-2012-00006-I.) AHRQ Publication No. 14-E004-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Office of Dietary Supplements/National Institutes of Health provided funding for this report.

The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Richard Kronick, Ph.D.
Director
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Christine Taylor, Ph.D.
Scientific Consultant, Office of Dietary Supplements
National Institutes of Health

Paul M. Coates, Ph.D.
Director, Office of Dietary Supplements
National Institutes of Health

Yen-pin Chiang, Ph.D.
Acting Deputy Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Aysegul Gozu, M.D., M.P.H.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Elizabeth A. Yetley, Ph.D.
Senior Nutrition Research Scientist, Retired
Office of Dietary Supplements
National Institutes of Health

Acknowledgments

We would like to thank Sean Rubin and Patricia Smith for their administrative support for the updated report. Additionally, we would like to thank Nono Ayivi-Guedehoussou, Dan Han, and Adeyemi Okunogbe for their support in helping with extracting the results data.

Technical Expert Panel

Glenville Jones, Ph.D.
Professor, Biochemistry and Medicine
Department of Biomedical & Molecular Sciences,
Queen's University
Kingston, Ontario, Canada
Scientific Advisory Board
Cytochroma Inc.
Markham, Ontario, Canada

Susan T. Mayne, Ph.D., F.A.C.E.
Department Chair and C.-E.A. Winslow Professor
Chronic Disease Epidemiology
Yale School of Public Health
Associate Director for Population Sciences Research
Yale Cancer Center
New Haven, CT

Clifford Rosen, M.D.
Senior Scientist
Maine Medical Center Research Institute
Scarborough, ME
Director of Clinical and Translational Research
Maine Medical Center
Portland, ME

Peer Reviewers

Patsy Brannon, Ph.D.
Professor, Division of Nutritional Sciences
Cornell University
Ithaca, NY

Kevin D. Cashman
Professor of Food and Health
School of Food & Nutritional Sciences
University College Cork
Cork, Ireland

J. Christopher Gallagher, M.D.
Professor of Endocrinology
Director of Bone Metabolism Unit
Creighton University
Omaha, NE

Michael F. Holick, Ph.D., M.D.
Professor of Medicine, Physiology, and Biophysics
Boston University School of Medicine
Boston, MA

Anne C. Looker, Ph.D.
National Center for Health Statistics
Centers for Disease Control and Prevention
Hyattsville, MD

Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update)

Structured Abstract

Background. In 2009, the Institute of Medicine/Food and Nutrition Board constituted a Dietary Reference Intakes (DRI) committee to undertake a review of the evidence that had emerged (since the 1997 DRI report) on the relationship of vitamin D and calcium, both individually and combined, to a wide range of health outcomes, and potential revision of the DRI values for these nutrients. To support that review, several United States and Canadian Federal Government agencies commissioned a systematic review of the scientific literature for use during the deliberations by the committee. The intent was to support a transparent literature review process and provide a foundation for subsequent reviews of the nutrients. The committee used the resulting literature review in their revision of the DRIs.

In 2013, in preparation for a project the National Institutes of Health Office of Dietary Supplements (NIH/ODS) was undertaking related to evidence-based decisionmaking for vitamin D in primary care, based on the updated DRI report, the ODS and AHRQ requested an update to the 2009 systematic review to incorporate the findings of studies conducted since the 2009 evidence review on the relationship between vitamin D alone or vitamin D plus calcium to selected health outcomes and to report on the methods used to assay vitamin D in the included trials.

Purpose. To systematically summarize the evidence on the relationship between vitamin D alone or in combination with calcium on selected health outcomes included in the earlier review: primarily those related to bone health, cardiovascular health, cancer, immune function, pregnancy, all-cause mortality, and vitamin D status; and to identify the vitamin D assay methods and procedures used for the interventional studies that aimed to assess the effect of vitamin D administration on serum 25(OH)D concentrations, and to stratify key outcomes by methods used to assay serum 25(OH)D concentrations.

Data sources. MEDLINE®; Cochrane Central; Cochrane Database of Systematic Reviews; and the Health Technology Assessments; search limited to English-language articles on humans.

Study selection. Primary interventional or prospective observational studies that reported outcomes of interest in human subjects in relation to vitamin D alone or in combination with calcium, as well as systematic reviews that met the inclusion and exclusion criteria.

Data extraction. A standardized protocol with predefined criteria was used to extract details on study design, interventions, outcomes, and study quality.

Data synthesis. We summarized 154 newly identified primary articles and two new systematic reviews that incorporated more than 93 additional primary articles. Available evidence focused mainly on bone health, cardiovascular diseases, or cancer outcomes. Findings were inconsistent across studies for bone health; breast, colorectal, and prostate cancer; cardiovascular disease and mortality; immune function; and pregnancy-related outcomes. Few studies assessed pancreatic cancer and birth outcomes. One new systematic review of observational studies found that

circulating 25(OH)D was generally inversely associated with risk for cardiovascular disease. Methods used to assay serum 25(OH)D in studies reporting on key outcomes diverged widely. The current report also identified one new systematic review published since the original report that addressed whether a dose response relationship exists between dietary and supplemental vitamin D intake and serum 25(OH)D concentrations. The systematic review, based on 76 RCTs, reported widely varying increases in serum concentrations of 25(OH)D for similar doses of vitamin D, with a general increase in serum concentration with dietary intake. The RCTs identified for the current report found increases in serum 25(OH)D with supplementation; however, the findings varied by age group and health status of participants, baseline vitamin D status, dose, duration, and assay used to assess serum 25(OH)D.

Limitations. Studies on vitamin D and calcium were not specifically targeted at life stages (except for pregnant and postmenopausal women) specified for the determination of DRI and were often underpowered for their intended outcomes. Studies vary widely in methodological quality and in the assays used to measure vitamin D status.

Conclusions. In solid agreement with the findings of the original report, the majority of the findings concerning vitamin D, alone or in combination with calcium, on the health outcomes of interest were inconsistent. Associations observed in prospective cohort and nested case-control studies were inconsistent, or when consistent, were rarely supported by the results of randomized controlled trials. Clear dose-response relationships between intakes of vitamin D and health outcomes were rarely observed. Although a large number of new studies (and longer followups to older studies) were identified, particularly for cardiovascular outcomes, all-cause mortality, several types of cancer, and intermediate outcomes for bone health, no firm conclusions can be drawn. Studies identified for the current report suggest a possible U-shaped association between serum 25(OH)D concentrations and both all-cause mortality and hypertension and also suggest that the level of supplemental vitamin D and calcium administered in the Women's Health Initiative Calcium-Vitamin D Trial are not associated with an increased risk for cardiovascular disease or cancer among postmenopausal women who are not taking additional supplemental vitamin D and calcium. Studies suggest the method used to assay 25(OH)D may influence the outcomes of dose-response assessments. Beyond these observations, it is difficult to make any substantive statements on the basis of the available evidence concerning the association of either serum 25(OH)D concentration, vitamin D supplementation, calcium intake, or the combination of both nutrients, with the various health outcomes because most of the findings were inconsistent.

Contents

Executive Summary ES-1
Introduction 1
Background 1
Sources, Metabolism and Functions of Vitamin D 2
Sources, Metabolism, and Functions of Calcium 5
Challenges for the DRI Committees 5
Key Questions Addressed in This Report 7
Methods 9
Overview 9
Sponsoring Federal Agencies 9
AHRQ Task Order Officer 9
Technical Expert Panel 9
EPC Methodologists 10
Development of the Analytic Framework and Refinement of Key Questions 10
Definitions 12
Vitamin D and Calcium Exposures 12
Clinical Outcomes 13
Indicators of Exposure (Nutrient Intake) 13
Surrogate Outcomes 13
Intermediate Outcomes 13
Life Stages 13
Key Questions 14
Literature Search Strategy 15
Study Selection 16
Abstract Screening 16
Full-Text Article Eligibility Criteria 16
Other Specific Eligibility Criteria 19
Data Extraction 20
Data Analysis 21
MetaAnalysis 22
Grading of Studies Analyzed in This Evidence Report 22
Critical Appraisal and Grading of Primary Studies 22
Grade A 23
Grade B 23
Grade C 23
Additional Considerations of Methodological Quality of Primary Studies for the Purpose of DRI Decisionmaking 24
Critical Appraisal of Systematic Reviews 24
Reporting of the Evidence 25
Evidence Tables 25
Summary Tables 25
Graphical Presentation of Dose-Response Relationship 25
Grand Summary Tables (Evidence Map) 25
Units of Measurement 26
Assay Method 26

Sunlight Exposure ... 26
Primary and Secondary Outcomes ... 27
Study Quality ... 27
Peer Review and Public Commentary ... 27
Results ... 28
Organization of the Results Section ... 28
Literature Search Results ... 28
Vitamin D and Health Outcomes ... 33
Vitamin D and Growth ... 33
Vitamin D and Cardiovascular Disease ... 48
Vitamin D and Body Weight ... 89
Vitamin D and Cancer ... 93
Vitamin D and Immunologic Outcomes ... 163
Vitamin D and Pregnancy-Related Outcomes ... 187
Vitamin D and Clinical Outcomes of Bone Health ... 199
Vitamin D and All-Cause Mortality ... 224
Vitamin D and Hypertension and Blood Pressure ... 242
Vitamin D and Bone Mineral Density or Bone Mineral Content ... 260
Combined Vitamin D and Calcium and Health Outcomes ... 273
Combined Vitamin D and Calcium and Growth ... 273
Combined Vitamin D and Calcium and Cardiovascular Disease ... 274
Combined Vitamin D and Calcium and Body Weight ... 280
Combined Vitamin D and Calcium and Cancer ... 284
Combined Vitamin D and Calcium and Pregnancy-Related Outcomes ... 295
Combined Vitamin D and Calcium and Clinical Outcomes of Bone Health ... 298
Combined Vitamin D and Calcium and All-Cause Mortality ... 306
Combined Vitamin D and Calcium and Hypertension and Blood Pressure ... 310
Combined Vitamin D and Calcium and Bone Mineral Density or Bone Mineral Content ... 317
How Does Dietary Intake of Vitamin D From Fortified Foods and Vitamin D Supplementation Affect Serum 25(OH)D Concentrations (Arrow 4)? ... 328
RCTs on Dietary Intakes of Vitamin D From Fortified Foods and Serum 25(OH)D Concentrations ... 328
RCTs on Vitamin D Supplementation and Serum 25(OH)D Concentrations ... 329
Stratification of Key Outcomes by Vitamin D Assay Method ... 339
Outcomes for Tolerable Upper Intake Levels ... 339
Renal Outcomes ... 339
Adverse Events Reported in RCTs ... 340
Discussion ... 346
Strengths of This Report ... 347
DRI and the Literature on Vitamin D and Calcium ... 348
Limitations of Our Methodological Approach ... 349
Comments on the Observational Studies ... 350
Sources of Heterogeneity and Potential Biases ... 351
Vitamin D Intake and Response in Serum 25(OH)D Concentration ... 351
Considerations for Future DRI Committees ... 352

References 353
Abbreviations 371
Latitudes of Selected Cities 374

Tables

Table A. Findings of the original report compared with the current report ES-21
Table 1. Number of primary studies on vitamin D intake or concentration and specific health outcomes that could be applicable to certain life stages [updated for the current report] 31
Table 2. Number of primary studies on calcium intake and specific health outcomes that could be applicable to certain life stages [not updated in the current report] 32
Table 3. Number of primary studies on combined vitamin D and calcium intake and specific health outcomes that are relevant to certain life stages [updated for the current report] 33
Table 4. Vitamin D and growth outcomes: Characteristics of interventional studies (updated from original report) 38
Table 5. Vitamin D and growth outcomes: Characteristics of cohort studies (updated from original report) 41
Table 6. Vitamin D and growth outcomes: Results of RCTs (updated from original report) 42
Table 7. Vitamin D and growth outcomes: Results of cohort studies (updated from original report) 45
Table 8. Vitamin D and cardiovascular outcomes: Characteristics of RCTs [no new studies in the current report] 54
Table 9. Vitamin D and cardiovascular outcomes: Results of RCTs [no new studies in the current report] 55
Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) 56
Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) 65
Table 11b. Vitamin D and cardiovascular outcomes: Results of nested case-control studies (new table) 80
Table 12. Vitamin D and weight: Characteristics of RCTs [no new studies in the current report] 91
Table 13. Vitamin D and weight: Results of RCTs [no new studies in the current report] 92
Table 14. Vitamin D and total cancer and total cancer mortality: Characteristics of RCTs [no new studies in the current report] 96
Table 15. Vitamin D and total cancer and total cancer mortality: Characteristics of cohort studies (updated from original report) 97
Table 16. Vitamin D and total cancer and total cancer mortality: Results of RCTs [no new studies in the current report] 100
Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report) 101
Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report) 110
Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report) 115
Table 20. Vitamin D and colorectal cancer: Characteristics of RCTs [no new studies in the current report] 123

Table 21. Vitamin D and colorectal cancer: Results of RCTs [no new studies in the current report] 124
Table 22. Vitamin D and colorectal cancer: Characteristics of observational studiesA (updated from original report) 128
Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) 132
Table 24. Vitamin D and colorectal adenoma: Characteristics of observational studies [no new studies in the current report] 143
Table 25. Vitamin D and colorectal adenoma: Results of observational studies [no new studies in the current report] 144
Table 26a. Vitamin D and breast cancer: Characteristics of nested case-control studies (updated from original report) 148
Table 26b. Vitamin D and breast cancer: Characteristics of prospective cohort studies (updated from original report) 150
Table 26c. Vitamin D and breast density: Characteristics of RCTs (updated from original report) 151
Table 26d Vitamin D and breast density: Characteristics of nested case-control studies (updated from original report) 151
Table 27a. Vitamin D and breast cancer: Results of nested case-control studies (updated from original report) 152
Table 27b. Vitamin D and breast cancer: Results of prospective cohort studies (updated from original report) 155
Table 27c. Vitamin D and breast density: Results of RCTs (updated from original report) 156
Table 27d. Vitamin D and breast density: Results of nested case-control studies (updated from original report) 157
Table 28. Vitamin D and pancreatic cancer: Characteristics of observational studies (updated from original report) 160
Table 29. Vitamin D and pancreatic cancer: Results of observational studies (updated from original report) 161
Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) 169
Table 30b. Vitamin D and immunologic outcomes: Characteristics of autoimmune disease RCTs (updated from original report) 176
Table 30c. Vitamin D and immunologic outcomes: Characteristics of infectious disease continuous RCTs (updated from original report) 176
Table 30d. Vitamin D and immunologic outcomes: Characteristics of infectious disease dichotomous RCTs (updated from original report) 177
Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report) 178
Table 31b. Vitamin D and immunologic outcomes: Results of autoimmune disease RCTs (updated from original report) 184
Table 31c. Vitamin D and immunologic outcomes: Results of infectious disease RCTs (continuous outcomes) (updated from original report) 184
Table 31d. Vitamin D and immunologic outcomes: Results of infectious disease RCTs (dichotomous outcomes) (updated from original report) 185

Table 32a. Vitamin D and preeclampsia: Characteristics of observational studies (updated from original report) 191
Table 32b. Vitamin D and other pregnancy outcomes: Characteristics of observational studies (updated from original report) 193
Table 32c. Vitamin D and preeclampsia: Characteristics of RCTs (updated from original report)..... 194
Table 33a. Vitamin D and preeclampsia: Results of observational studies (updated from original report) 195
Table 33b. Vitamin D and other pregnancy outcomes: Results of observational studies (updated from original report) 197
Table 33c. Vitamin D and preeclampsia: results of RCTs (updated from original report) 198
Table 34. Summary of systematic review of the effect of vitamin D on bone health (not updated from original report) 201
Table 35a. Vitamin D and bone health: Characteristics of RCTs published after the Ottawa EPC report (updated from original report)..... 206
Table 35b. Vitamin D and muscle strength: Characteristics of RCTs (updated from original report)..... 207
Table 35c. Vitamin D and muscle strength: Characteristics of prospective cohorts (updated from original report) 208
Table 35d. Vitamin D and bone health: Characteristics of observational studies published after the Ottawa EPC report (updated from original report)..... 209
Table 36a. Vitamin D and bone health: Results of RCTs published after the Ottawa EPC report (updated from original report)..... 212
Table 36b. Vitamin D and muscle strength: Results of RCTs (updated from original report)..... 214
Table 36c. Vitamin D and muscle strength: Results of prospective cohorts (updated from original report) 217
Table 36d. Vitamin D and bone health: Results of observational studies published after the Ottawa EPC report (updated from original report)..... 221
Table 37. Summary of systematic review on vitamin D supplementation and all-cause mortality (not updated from original report)..... 225
Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report) 228
Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) 233
Table 40. Vitamin D and hypertension: Characteristics of cohort studies (updated from original report) 245
Table 41. Vitamin D and hypertension: Results of cohort and nested case-control studies (updated from original report) 246
Table 42. Vitamin D and blood pressure: Characteristics of RCTs (updated from original report)..... 251
Table 43. Vitamin D and blood pressure: Results of RCTs..... 255
Table 44. Vitamin D and bone mineral density: Characteristics of RCTs published after the Ottawa EPC report (updated from original report)..... 264
Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report) 267

Table 46. Combined vitamin D and calcium and cardiovascular outcomes: Characteristics of RCTs (formerly Table 85) (updated from original report) 277
Table 47. Combined vitamin D and calcium and cardiovascular outcomes: Results of RCTs (formerly Table 86) (updated from original report) 278
Table 48. Combined vitamin D and calcium and weight: Characteristics of RCTs (formerly Table 87) (no new studies in the current report) 282
Table 49. Combined vitamin D and calcium and weight: Results of RCTs (formerly Table 88) [no new studies in the current report] 283
Table 50. Combined vitamin D and calcium and total cancer incidence: Characteristics of RCTs (formerly Table 89) (updated from original report) 285
Table 51. Combined vitamin D and calcium and total cancer incidence: Results of RCTs (formerly Table 90) (updated from original report) 286
Table 52. Combined vitamin D with calcium and colorectal cancer: Characteristics of RCTs (formerly Table 91) [no new studies in the current report] 289
Table 53. Combined vitamin D with calcium and colorectal cancer: Results of RCTs (formerly Table 92) [no new studies in the current report] 290
Table 54. Combined vitamin D and calcium and breast cancer outcomes: Characteristics of RCTs (formerly Table 93) [no new studies in the current report] 293
Table 55. Combined vitamin D and calcium and breast cancer outcomes: Results of RCTs (formerly Table 94) [no new studies in the current report] 294
Table 56. Combined vitamin D and calcium and preeclampsia: Characteristics of RCTs (formerly Table 95) [no new studies in the current report] 296
Table 57. Combined vitamin D and calcium and preeclampsia: Results of RCTs (formerly Table 96) [no new studies in the current report] 297
Table 58. Combined vitamin D and calcium and bone health: Characteristics of RCTs published after the Ottawa EPC report (formerly Table 97) (updated from original report) 301
Table 59. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (stress fracture) (formerly Table 98) (updated from original report) 302
Table 60. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (performance measures) (formerly Table 99) (updated from original report) 305
Table 61. Combined vitamin D and calcium and incident hypertension: Characteristics of RCTs [no new studies in the current report] 311
Table 62. Combined vitamin D and calcium and incident hypertension: Results of RCTs [no new studies in the current report] 312
Table 63. Combined vitamin D and calcium and blood pressure: Characteristics of RCTs (formerly Table 102) [no new studies in the current report] 315
Table 64. Combined vitamin D and calcium and blood pressure: Results of RCTs (formerly Table 103) [no new studies in the current report] 316
Table 65. Combined vitamin D and calcium and bone mineral density/content: Characteristics of RCTs published after the Ottawa EPC report (formerly Table 104) (no new studies in the current report) 320
Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) (no new studies in the current report) 322

Table 67. The relationship between vitamin D3 daily doses and changes in 25(OH)D concentrations in RCTs (formerly Table 106) (updated from original report) 336
Table 68. Adverse events reported in RCTs (formerly Table 107) (updated from original report) 342

Figures

Figure 1. Summary of the vitamin D endocrine system [updated figure for the current report] 4
Figure 2. Generic analytic framework to assist formulation of Key Questions for the development of DRIs. 8
Figure 3. Analytic framework for vitamin D with or without calcium: EARs [revised for the current report] 11
Figure 4. Analytic framework for vitamin D with or without calcium ULs [revised for the current report] 12
Figure 5a. Literature flow for the original report 29
Figure 5b. Literature flow for the current report 30
Figure 6a. Cardiovascular outcomes risk stratified by vitamin D concentration for combined and general CV outcomes 81
Figure 6b. Cardiovascular outcomes risk stratified by vitamin D concentration for combined and general CV outcomes by gender 82
Figure 6c. Cardiovascular outcomes risk stratified by vitamin D concentration for CV mortality 83
Figure 6d. Cardiovascular outcomes risk stratified by vitamin D concentration for CV mortality by gender 84
Figure 6e. Cardiovascular outcomes risk stratified by vitamin D concentration for myocardial infarction 85
Figure 6g. Cardiovascular outcomes risk stratified by vitamin D concentration for fatal stroke 87
Figure 6h. Cardiovascular outcomes risk stratified by vitamin D concentration for congestive heart failure 88
Figure 7. Prostate cancer risk stratified by vitamin D concentration (updated from original report) 121
Figure 8. Colorectal cancer risk stratified by vitamin D concentration 139
Figure 9. Colon cancer risk stratified by vitamin D concentration 140
Figure 10. Rectal cancer risk stratified by vitamin D concentration 141
Figure 11. Forest plot of trials of combined vitamin D and calcium supplementation and effects on all-cause mortality (formerly Figure 22) 309
Figure 12. Relationship between doses of vitamin D3 supplementation and net changes in serum 25(OH)D concentrations in RCTs (formerly Figure 23) 332
Figure 13. Relationship between doses of vitamin D3 supplementation and net changes in serum 25(OH)D concentrations in RCTs by baseline vitamin D status among adults (formerly Figure 24) 333
Figure 14. Relationship between doses of vitamin D3 supplementation and net changes in serum 25(OH)D concentrations in RCTs by duration of supplementation among adults (formerly Figure 25) 334
Figure 15. Relationship between doses of vitamin D3 supplementation and net changes in serum 25(OH)D concentrations in RCTs by assay type (new figure) 335

Appendixes

Appendix A. Search Strategy for Primary Studies
Appendix B. Search Strategy for Systematic Reviews
Appendix C. Evidence Tables for the Current Report
Appendix D. Evaluation of Existing Systematic Reviews and Evidence Tables of the Qualified Systematic Reviews
Appendix E. Blank Data Extraction Form and Quality Assessment Checklists
Appendix F. Excluded Studies
Appendix G. Serum Vitamin D Assay Reporting in Randomized Controlled Trials (RCTs)
Appendix H. Studies Reporting Key Outcomes Stratified by Vitamin D Assay Method

Executive Summary

Background

In 2009, the Tufts Evidence-based Practice Center (EPC) conducted a systematic review of the scientific literature on vitamin D and calcium intakes as related to status indicators and health outcomes. The purpose of this report was to guide the nutrition recommendations of the Institute of Medicine (IOM) Dietary Reference Intakes (DRIs).

In September 2007, the IOM held a conference to examine the lessons learned from developing DRIs, and future challenges and best practices for developing DRIs. The conference concluded that systematic reviews would enhance the transparency and rigor of DRI committee deliberations. With this framework in mind, the Agency for Healthcare Research and Quality (AHRQ) EPC program invited the Tufts EPC to perform the systematic review of vitamin D and calcium.

In May and September 2007, two conferences were held on the effect of vitamin D on health. Subsequently, a working group of scientists from the United States and Canadian Governments convened to determine whether enough new research had been published since the 1997 vitamin D DRI to justify an update. Upon reviewing the conference proceedings and results from a recent systematic review, the group concluded that sufficient new data beyond bone health had been published. Areas of possible relevance included new data on bone health for several of the life stage groups, reports on potential adverse effects, dose-response relations between intakes and circulating 25-hydroxyvitamin D (25(OH)D) concentrations and between 25(OH)D concentrations, and several health outcomes.

In 2013, in preparation for a project the National Institutes of Health Office of Dietary Supplements (NIH/ODS) was undertaking related to evidence-based decisionmaking for vitamin D in primary care, which will include information from this updated systematic review on vitamin D and health outcomes, the ODS and AHRQ requested an update to the 2009 systematic review that will incorporate the findings of studies on vitamin D and vitamin D administered in conjunction with calcium that have been conducted since the release of the 2009 review. This updated report assesses all outcomes assessed in the original 2009 report (for vitamin D and vitamin D plus calcium) with the exception of outcomes pertaining to body weight and composition and postnatal growth. This updated report also describes the assay methodologies used in trials included in the original review as well as any newly included studies that report on the effect of vitamin D supplementation on serum 25(OH)D concentrations, to permit a comparison of dose-response outcomes by assay method. The text of the original 2009 report has been preserved essentially in its entirety: Text and tables that report outcomes of calcium supplementation only have been omitted. Here and in the remainder of the report, updated methods, study details, and findings are presented in boldface type. The protocol for the updated report was posted on the AHRQ Web site for public comment, which can be found at http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1529.

This update was requested by the sponsor in anticipation of a conference focused on the evaluation of evidence related to vitamin D and health outcomes, but the update can also be helpful to other stakeholders. The sponsor's interest was to determine whether the inclusion of newer relevant data that became available during the period following the close of the 2009 review would alter or continue to support the conclusions of the 2009

report. The sponsor's interest did not include the topic area of calcium alone or of growth and body weight as they relate to vitamin D, so for reasons of cost these components of the original report were not included in this review.

The **original** report included a systematic review of health outcomes relating to vitamin D and calcium intakes, both alone and in combination; **the current report updates that systematic review for outcomes relating to intakes of vitamin D alone or in combination with calcium**. The executive summary provides a high-level overview of the findings of the systematic review; **the summary of studies included in the current report is in boldface type**. Recommendations and potential revisions of nutrient reference values (i.e., the new DRIs) based on this review are the responsibility of the IOM committee and are beyond the scope of this report.

Methods

This systematic review—**both the original and the update**—answers key scientific questions on how dietary vitamin D and calcium intakes affect health outcomes. Federal sponsors defined the Key Questions, and a technical expert panel was assembled to refine the questions and establish inclusion and exclusion criteria for the studies to be reviewed. In answering the questions, we followed the general methodologies described in AHRQ's "Methods Guide for Comparative Effectiveness Reviews." The **original** report **was** provided to an IOM committee charged with updating vitamin D and calcium DRIs. **The current report will be made available to NIH/ODS, which are the sponsors of this update. Neither** this report **nor the original** makes clinical or policy recommendations.

The population of interest is the "general population" of otherwise healthy people to whom DRI recommendations are applicable. The Key Questions addressed in **the original report and** this **updated** report are as follows:

Key Question 1. What is the effect of vitamin D, calcium (**excluded from current/updated report)**, or combined vitamin D and calcium intakes on clinical outcomes, including growth, cardiovascular diseases, body weight outcomes, cancer, immune function, pregnancy or birth outcomes, mortality, fracture, renal outcomes, and soft tissue calcification (**the current report excludes the outcomes of postnatal growth and weight outcomes)**?

Key Question 2. What is the effect of vitamin D, calcium **(excluded from current report),** or combined vitamin D and calcium intakes on surrogate or intermediate outcomes, such as hypertension, blood pressure, and bone mineral density?

Key Question 3. What is the association between serum 25(OH)D concentrations or calcium balance **(excluded from current report)** and clinical outcomes?

Key Question 4. What is the effect of vitamin D or combined vitamin D and calcium intakes on serum 25(OH)D concentrations?

Key Question 5. What is the association between serum 25(OH)D concentrations and surrogate or intermediate outcomes?

The original report performed electronic searches of the medical literature (1969–April 2009) to identify publications addressing the aforementioned questions. We set specific eligibility criteria. We reviewed primary studies and existing systematic reviews. When a qualifying systematic review was available, we generally relied on the systematic review, and updated it by reviewing studies published after its completion. **The search strategy of peer-reviewed literature for the updated report duplicated that used in the original 2009 report to the extent possible, excluding the searches specific to calcium only and those for the outcomes of growth and weight. Searches for the current report covered the time period from January 2008 to April 2013.**

We rated the primary studies using a three-grade system (A, B, or C), evaluating each type of study design (i.e., randomized controlled trial or RCT, cohort, and nested case-control). Grade A studies have the least bias, and their results are considered valid within the limits of interpretation for that study design. Grade B studies are susceptible to some bias, but the amount is not sufficient to invalidate the results. Grade C studies have significant bias that may invalidate the results.

Results

The original report screened for eligibility a total of 18,479 citations that were identified through our searches, perusal of reference lists, and suggestions from experts. Of 652 publications that were reviewed in full text, 165 primary study articles and 11 systematic reviews were included in the systematic review. Their results are summarized in this report.

For the current report, we screened for eligibility a total of 6,165 citations identified through electronic searches, reference mining, and handsearches for articles suggested by experts. Of 1,107 publications reviewed in full text, 154 new articles (reporting on 156 studies) and two existing systematic reviews were included in this systematic review. The results are summarized in this report in boldface type. Table A summarizes the numbers of studies included for each outcome for both the original and the current report, stratified by study design, as well as the conclusions.

Vitamin D

Vitamin D and Growth

For the current report, we identified five new RCTs (reported in four articles) and two new observational studies that evaluated intake of or exposure to vitamin D, respectively, on birth weight and/or length. In the current report, five RCTs (reported in four articles) reported on the effect of vitamin D supplementation during pregnancy on birth weight and/or length. One U.S. RCT divided 350 women who were already receiving prenatal vitamins that provided 400 international units (IU) vitamin D per day at 16 weeks gestation

or earlier into three groups, who were given an additional 0, 1,600, or 3,600 IU vitamin D per day through the remainder of gestation; the study found no difference in birth weight among interventional arms (rated A).[1] The second study, a pseudo-RCT conducted in India, divided 140 pregnant women at 12 to 24 weeks gestation into two groups: one was administered one 1,500 microgram dose of vitamin D and the other received two doses of 3,000 micrograms vitamin D (a group of untreated women who were 24 weeks pregnant or more served as the controls); both of the treated groups gave birth to infants who were significantly heavier than the usual care group (p=0.003) (rated C). The third RCT, the AViDD study conducted in Bangladesh, randomly divided 160 women at 26 to less than 30 weeks gestation to receive 35,000 IU vitamin D per week or no supplement; no difference was seen in birth weight or length, although the study was not powered to see differences in these outcomes (rated A). For the fourth and fifth studies, data from the National Institute of Child Health and Disease (NICHD) and Thrasher Research Fund Vitamin D_3 Supplementation studies—in which pregnant women were randomized to receive 0, 2,000, or 4,000 IU vitamin D per day in addition to their prenatal vitamins—were analyzed in combination: No differences were observed in birth weight among the groups (rated B). Of the two observational cohort studies, one observed a significant association of second trimester maternal vitamin D concentrations (rated B) and one found no association (rated A).

As reviewed in the original report, six RCTs, one nonrandomized comparative intervention study, and two observational studies evaluated intake of vitamin D or serum 25(OH)D concentrations and growth parameters in infants and children. The studies had diverse populations and methodological approaches. One RCT and one observational study were rated B; seven studies were rated C. Most studies found no significant associations between either maternal or offspring vitamin D intake and offspring's weight or height, but two C-rated intervention studies from the same center in India found a significant effect of total maternal vitamin D intake of 1.2 million IU and increased infant birth weights.

Vitamin D and Cardiovascular Events

One good-quality existing systematic review of prospective studies identified for the current report found a significant association between low serum 25(OH)D concentrations and a number of clinical cardiovascular outcomes, including total cardiovascular disease, coronary heart disease, cardiovascular disease mortality, and stroke. No RCTs were identified for the current report that evaluated the effects of vitamin D on clinical cardiovascular disease outcomes. New observational studies identified for the current report (7 for total cardiovascular events, 17 for cardiovascular death, 2 for ischemic heart disease, 6 for myocardial infarction, 8 for stroke, and 3 for fatal stroke) found mixed associations between 25(OH)D and all of these outcomes.

As reviewed in the original report, one B-rated RCT and four cohort studies (two rated A, two C) have analyzed the association between serum 25(OH)D concentrations and risk of cardiovascular events. The RCT, which compared vitamin D_3 (100,000 IU every 4 months) or placebo for 5 years in elderly people, found no significant difference in event rates for various cardiovascular outcomes, including total events and cardiovascular deaths. In two of the cohort studies, significant associations were found between progressively lower 25(OH)D concentration—analyzed at upper thresholds of 37.5 and 75 nmol/L—and progressively increased risk of any cardiovascular event. The other two cohort studies found no significant

associations between serum 25(OH)D concentrations and cardiovascular death, myocardial infarction, or stroke.

Vitamin D and Body Weight

The current report did not assess the association between vitamin D and body weight. For the original report, no studies evaluated serum 25(OH)D concentrations and risk of obesity or overweight. We evaluated only RCTs for changes in body weight. Three RCTs (one rated B, two rated C) compared a range of dosages (300 IU/d to 120,000 IU every 2 weeks) to placebo. Vitamin D supplementation had no significant effect on weight.

Vitamin D and Cancer

Cancer From All Causes

No new RCTs were identified for the current report that addressed the effect of vitamin D or vitamin D combined with calcium on the risk for total cancer or cancer mortality. Two new cohort studies found no association between total (all-cause) cancer incidence and serum 25(OH)D concentrations (rated A and B). Ten new cohort studies and one new nested case-control study addressed the association of serum 25(OH)D concentrations and cancer mortality. Five of the cohort studies (one rated A, four rated B) observed no association of serum 25(OH)D concentration with total cancer mortality. Three cohort studies and the nested case-control study observed a trend toward increased risk with decreased serum 25(OH)D (all rated B). One analysis using updated Third National Health and Nutrition Examination Survey (NHANES III) data (rated B) observed a trend toward increasing risk for death with increasing serum 25(OH)D among men at higher latitudes whose blood was drawn in summer but the reverse in women. One cohort study observed a U-shaped association of increasing mortality with both low and high serum 25(OH)D.

The original report identified two B-rated RCTs and an analysis of the NHANES database (two publications, rated B and C). Both RCTs were conducted in older adults (postmenopausal women in one and people >70 years in the other). They found no significant effects for vitamin D supplementation (approximately 1,500 IUs per day or 100,000 IU every 4 months). Analyses of NHANES III showed no significant association between baseline serum 25(OH)D concentrations and total cancer mortality.

Prostate Cancer

In the current report, four new nested case-control studies (two rated A, two rated B) and one new prospective cohort study (rated B) found no association between baseline serum 25(OH)D concentrations and risk for prostate cancer. Two new nested case-control studies (both rated B) observed a trend between higher serum vitamin D concentrations and increasing risk for prostate cancer. In one study this increase was seen only among men whose sera were sampled in summer or autumn; in the other study, this trend was observed only when participants were divided by quartiles of 25(OH)D concentration, but not when they were divided by categories of vitamin D sufficiency (concentrations less than 50 nmol/L being considered deficient, 50–75 nmol/L insufficient, and 75–125 nmol/L considered sufficient).

In the original report, 12 nested case-control studies (3 rated B, 9 C) evaluated the association of baseline serum 25(OH)D concentrations and prostate cancer risk. No eligible

RCTs were identified. Eight of the nested case-control studies found no statistically significant dose-response relationship between serum 25(OH)D concentrations and the risk of prostate cancer. One C-rated study found a significant association between lower baseline serum 25(OH)D concentrations (<30 compared with >55 nmol/L) and higher risk of prostate cancer. Another C-rated study suggested the possibility of a U-shaped association between baseline serum 25(OH)D concentrations and the risk of prostate cancer (i.e., lower and higher serum 25(OH)D concentrations were associated with an increased risk of prostate cancer compared with that of the in between reference level).

Colorectal Cancer

No new RCTs and cohort studies that addressed the effect of vitamin D on colorectal cancer mortality or incidence were identified for the current report. Three new nested case-control studies (two rated A, one rated B) found trends of increasing colorectal cancer incidence with decreasing 25(OH)D concentrations. One nested case-control study (rated B) found no association between colorectal cancer and 25(OH)D. Two of these nested case-control studies (both rated B) also examined colon and rectal cancer as separate outcomes. One study reported a significant negative trend between 25(OH)D and colon cancer risk and the other found a nonsignificant negative trend. For rectal cancer, the same two studies reported either a negative trend or a small but nonsignificant negative trend with 25(OH)D.

The original report identified one B-rated RCT, one B-rated cohort study, and seven nested case-control studies (five rated B, two C) that evaluated the association between vitamin D exposure and colorectal cancer. The RCT of elderly population reported no significant difference in colorectal cancer incidence or mortality with or without vitamin D_3 supplements over 5 years of followup. Most nested case-control studies found no significant associations between serum 25(OH)D concentrations and risk of colorectal cancer incidence or mortality. However, two of the three B-rated nested case-control studies in women found statistically significant trends between higher serum 25(OH)D concentrations and lower risk of colorectal cancer, but no individual quantile of serum 25(OH)D concentration had a significantly increased risk of colorectal cancer (compared with the reference quantile). The B-rated cohort study of women also suggested an association between higher serum 25(OH)D concentrations (>50 nmol/L) and lower risk of colorectal cancer mortality. The studies of men or of both sexes, and of specific cancers, did not have consistent findings of associations.

Colorectal Polyps

No new studies were identified for the current report that assessed the association between colorectal polyps and serum concentrations of 25(OH)D.

For the original report, one B-rated nested case-control study in women found no significant association between serum 25(OH)D concentrations and risk of colorectal polyps. No RCTs evaluated this outcome.

Breast Cancer

Eight new observational studies that assessed the association between 25(OH)D and breast cancer were identified for the current report. Two cohort and four nested case-control studies found no association (three rated A, three rated B). Two nested case-control

studies found increasing risk of breast cancer with decreasing 25(OH) concentrations (both rated B).

One new observational study that assessed the association between 25(OH)D and breast cancer-specific mortality was also identified. This cohort study found no association (rated B).

Two new studies, an RCT that examined the effect of vitamin D and calcium intake on breast density and a nested case-control study that assessed the association of serum 25(OH)D with breast density, were identified. The RCT found a decrease in percent mammographic density among women who had greater than or equal to 400 IU per day total vitamin D intake (rated A). The nested case-control found lower risk of increased mammographic density with 25(OH) concentrations above the first quartile (rated B).

In the original report, one cohort compared serum 25(OH)D concentrations and the risk of breast cancer mortality, and two nested case-control studies compared 25(OH)D concentrations and the incidence of breast cancer. All three studies were rated B. The NHANES III analysis reported a significant decrease in breast cancer mortality during 9 years of followup in those with baseline serum 25(OH)D concentration greater than 62 nmol/L. However, during 7 to 12 years of followup, the nested case-control studies found no significant relationship between serum 25(OH)D concentration and risk of breast cancer diagnosis in either premenopausal or postmenopausal women.

Pancreatic Cancer

For the current report, a new pooled nested case-control study within eight cohorts found an association between 25(OH)D concentration and pancreatic cancer (rated B). Individuals with 25(OH)D concentration greater than or equal to 100 nmol/L had greater risk of pancreatic cancer incidence compared with those with 25(OH)D less than 25 nmol/L.

For the original report, two A-rated nested case-control studies evaluated the association of serum 25(OH)D concentrations and pancreatic cancer. No relevant RCTs were identified. One study of male smokers found a statistically significant relationship between increasing serum 25(OH)D concentration (>65.5 vs. <32 nmol/L) and higher risk for pancreatic cancer, and the subanalysis of the second study found an increased risk of pancreatic cancer among study participants with higher 25(OH)D concentrations (>78.4 nmol/L) compared with lower (<49.3 nmol/L) concentrations only in those living in low residential ultraviolet B exposure areas.

Vitamin D and Immunologic Outcomes

The current report identified four new RCTs that assessed the effect of supplemental vitamin D on infectious illnesses and nine cohort studies that assessed the association between serum 25(OH)D concentrations and risk for infectious illnesses. RCTs of infants and adults reported no significant effect of supplementation on the risk for upper respiratory infections (one rated A; three rated B). Three new prospective cohort studies observed an association between low cord blood 25(OH)D concentrations and increased risk for respiratory infections at 3 to 6 months of age, in New Zealand, China, and the Netherlands, respectively (all rated B). Two studies of school-age children observed inverse associations of serum 25(OH)D and risks for various infectious illnesses (both rated B). ("Inverse association" refers to an association between lower serum 25(OH)D concentrations and a higher risk for the outcome of interest; "association" or "positive

association" refers to an association between higher serum 25(OH)D concentration and a higher risk for the outcome.) A study of healthy U.S. adults found an association between serum concentrations of 25(OH)D levels of 95 nmol/L or higher and reduced risk for acute respiratory viral infections (rated B). One study of adults observed an inverse association of serum 25(OH)D with risk for respiratory disease mortality, and another observed an inverse association with risk for pneumonia (both rated B).

The report identified one new RCT that found no effect of prenatal vitamin D supplementation on the risk for wheeze, atopy, and eczema (rated A). The report also identified five new prospective cohort/nested case-control studies that reported mixed associations of serum concentrations of 25(OH)D and risk for asthma, atopy, and/or eczema. An Australian study observed a significant association of cord blood 25(OH)D and risk for eczema but not allergies at 12 months of age. A prospective cohort study conducted in the United Kingdom found no association between maternal serum 25(OH)D at 34 weeks gestation and asthma, wheeze, and atopy in their children at 6 years of age. A prospective cohort study conducted in the Netherlands found that serum 25(OH)D concentrations at 4 years of age significantly predicted asthma and severe asthma at 8 years of age. Another United Kingdom longitudinal study found a small but statistically significant association of wheeze and antecubital dermatitis in 10-year old children with serum levels of 25(OH)D_2 but a negative association with 25(OH)D_3. Finally, the HUNT study, a large population health survey in Norway, found no association of vitamin D with asthma in women and only a weak association in men that disappeared when adjusted for confounders.

The current report identified one new RCT and four new prospective cohort studies on the risk for autoimmune disease. A substudy of the Women's Health Initiative (WHI) calcium/vitamin D (CaD) trial found no effect of supplementation on women's risk for rheumatoid arthritis (rated A). Two nested case-control studies and one cohort study assessed the association between maternal serum 25(OH)D concentrations or subsequent childhood or adult concentrations with risk for type 1 diabetes mellitus and reported mixed findings (one each rated A, B, and C). One study assessed the effects of maternal serum 25(OH)D concentrations on the risk for multiple sclerosis (MS) in the offspring and also assessed the effect of serum 25(OH)D concentrations across the adult population on the risk for subsequent MS and found mixed effects (rated B).

For the original report, two C-rated cohort studies, but no RCTs, evaluated immunologic outcomes. NHANES III found no significant association between serum 25(OH)D concentrations and infectious disease mortality. Another cohort study suggested a possible relationship between higher maternal 25(OH)D concentration (>50 nmol/L) and increased risk of eczema in their children, but the analysis did not control for important confounders, and the 25(OH)D concentrations in the children were not measured.

Vitamin D and Pregnancy-Related Outcomes

Preeclampsia

For the current report, we identified one article that reported on two combined RCTs assessing the effect of supplemental vitamin D on the risk for preeclampsia: Supplementation with 4,000 IU per day decreased the risk for preeclampsia. We also identified five new nested case-control studies and two prospective cohort studies (all rated B), of which three of the nested case-control studies and the two prospective case-control

studies observed an association between 25(OH)D concentrations less than 50 nmol/L and preeclampsia or severe preeclampsia. The other two nested case-control studies (the Canadian EMMA study and a U.S. study) observed no association between low first trimester maternal 25(OH)D levels and severe preeclampsia.

In the original report, one B-rated nested case-cohort study found an association between low 25(OH)D concentration (<37.5 nmol/L) early in pregnancy and preeclampsia.

Other Outcomes

In the current report, we identified two new cohort studies that assessed the association between maternal serum 25(OH)D concentrations and the risk for giving birth to a small-for-gestational-age (SGA) infant and one new nested case-control study and one prospective cohort study that assessed the association with preterm birth. One of the two cohort studies found an increase in the incidence of SGA at the lowest concentration range of maternal serum 25(OH)D compared with higher serum vitamin D concentrations for both white and black mothers (study rated B). The other cohort study, which assessed 412 mother-infant pairs, found a U-shaped association between serum 25(OH)D and incidence of SGA among white mothers. The lowest risk was observed from 60 to 80 nmol/L; compared with serum 25(OH)D 37.5–75 nmol/L, SGA odds ratios (95% CI) for levels, 37.5 and 0.75 nmol/L were 7.5 (1.8, 31.9) and 2.1 (1.2, 3.8); this association was not seen among black mothers (study rated A).

The nested case-control study that assessed the association with preterm birth found no significant association (rated B), whereas the prospective cohort study did observe an association between lower prenatal serum 25(OH)D concentrations and the risk for preterm birth among women carrying twins (rated A).

We found no new studies for the current report on the relationship of maternal serum 25(OH)D and pregnancy hypertension.

The original report did not identify any eligible studies on the relationship of vitamin D and maternal hypertension, preterm birth, or small infant for gestational age.

Vitamin D and Bone Health

The results reported in this section are based on the Ottawa EPC Evidence Report "Effectiveness and safety of vitamin D in relation to bone health" and on our updated literature review of studies published after its completion.

Rickets

No new studies assessing the association between vitamin D supplementation and the risk for rickets met the inclusion criteria for the current report.

The original report cited the Ottawa EPC report for these outcomes. The Ottawa EPC report concluded that there is "fair" evidence, regardless of the type of assay, for an association between low serum 25(OH)D concentrations and confirmed rickets. According to the report, there is inconsistent evidence regarding the threshold concentration of serum 25(OH)D, above which rickets does not occur.

Our updated search did not identify new studies examining the association between vitamin D and rickets.

Fractures, Falls, or Performance Measures of Strength

The current report did not identify any new RCTs that assessed the effect of interventions of vitamin D alone on fracture risk. We identified two new RCTs that examined the effect of supplementation with vitamin D on the risk for falls, two new RCTs on muscle strength, and six new observational studies that assessed the association between serum 25(OH)D and fracture risk; results were inconsistent among them.

Two RCTs were identified for the current report that examined the effects of vitamin D supplementation on the risk for falls among older adults (both rated A). One trial found a small effect, and one found reductions only in particular groups of fallers.

Two RCTs were identified for the current report that examined the effects of 1 year of vitamin D supplementation on muscle strength (both rated A). One RCT showed positive effects among older adults, and one study showed effects only among the participants with lower serum 25(OH) D concentrations at baseline.

Four prospective cohort studies assessed the association between serum 25(OH)D concentrations and muscle strength, and one prospective cohort study assessed the association between serum 2(OH)D and falls. Three of the four prospective cohort studies reported associations between lower serum 25(OH)D and decreased or decreasing muscle strength and performance (one rated A, one rated B, one rated C); a fourth cohort study saw no association with faster rate of decline in muscle function (rated B). An association was seen between lower 25(OH)D concentrations and increased risk for falls over a year (study rated B).

We identified eight prospective cohort and nested case-control studies that assessed the association between 25(OH)D status and fracture risk. Three studies that assessed risk for hip fracture at 6 to 11 years followup (one rated A and two rated B) had mixed results.

Two large-scale studies with B ratings, one among older men and one among older adults of both sexes, found no association of serum 25(OH)D concentration and risk for nonvertebral fracture. Followups to two other large-scale studies, both with A ratings, reported serum 25(OH)D to be a significant predictor of hip fracture and other major osteoporotic fractures in older adults.

Two studies that assessed total fragility fracture (one rated A and one rated B), both in postmenopausal women, also reported inconsistent results.

As described in the original report, the Ottawa EPC report concluded that the associations between serum 25(OH)D concentrations and risk of fractures, falls, and performance measures of strength among postmenopausal women or elderly men are inconsistent.

Findings from three additional C-rated RCTs reported no significant effects of vitamin D supplementation (dosage range 400–822 IU/d) in reducing the risk of total fractures or falls in adults older than 70 years.

Bone Mineral Density or Bone Mineral Content

To assess the effect of vitamin D on bone mineral content or density, we included only RCTs. Eight new RCTs identified for the current report assessed the effects of supplemental vitamin D alone on bone mineral content (BMC) or density (BMD). One of the eight, a study in infants (rated A), showed a trend toward increasing BMC. A second study, in postmenopausal women, found that 1,000 IU vitamin D per day reduced loss of BMD at the hip compared with no or 400 IU per day supplementation, but no effect was seen on spinal BMD (study rated A). Six RCTs, two in teen girls and the remaining four in

adults of both sexes (one rated A, four rated B, and one rated C) showed no effect of vitamin D supplementation for as much as 2 years on BMD.

As described in the original report, the Ottawa EPC report concluded that observational studies suggested a correlation between higher serum 25(OH)D concentrations and larger values of BMC indices for older children and adolescents (6 months through 18 years old). In addition, there was "fair" evidence among observational studies of postmenopausal women and elderly men to support an association between higher serum 25(OH)D and higher BMD or increases in BMD at the femoral neck. However, there was discordance between the results from RCTs and the majority of observational studies.

For this outcome, we included only RCTs for our update literature review. Consistent with the findings of RCTs in the Ottawa EPC report, the three additional RCTs (one rated A, one B, one C) showed no significant effects of vitamin D supplementation on BMC in children or BMD in adults.

Vitamin D and All-Cause Mortality

No new RCTs were identified for the current report that assessed the effect of vitamin D supplementation on risk for all-cause mortality. The current report identified 25 new articles that assessed the association between serum 25(OH)D concentration and risk for all-cause mortality. Of the 25, 7 found no association (1 rated A, 6 rated B), 16 found an association of lower serum 25(OH)D concentrations with increased risk for mortality (6 rated A, 9 rated B: 1 article reported on 2 studies), and 2 reported an association of both higher and lower 25(OH)D concentrations with increased mortality risk (rated A and B).

The assessment of the literature on vitamin D and all-cause mortality in the original report was based on a reanalysis of an existing systematic review and metaanalysis of RCTs on vitamin D supplementation for mortality. One additional C-rated RCT was identified. Four additional cohort studies (one rated B, three C) on the association of vitamin D and all-cause mortality also qualified. Four RCTs (N=13,899) were included in the reanalysis of the systematic review. In each study, mean age was older than70 years and dosages ranged between 400 to 880 IU per day. Vitamin D supplementation had no significant effect on all-cause mortality (summary relative risk [RR]=0.97, 95% CI 0.92, 1.02; random effects model). There is little evidence for between-study heterogeneity in these analyses. Three of the cohort studies found no significant association between 25(OH)D concentrations and all-cause mortality, but one found a significant trend for lower odds of death with increasing 25(OH)D concentrations, greater than 23 nmol/L in men and greater than 19 nmol/L in women.

Vitamin D and Hypertension and Blood Pressure

Hypertension

For the current report we identified no new RCTs that addressed the relationship of serum 25(OH)D concentrations or supplementation with hypertension. A large prospective cohort study identified for the current report that evaluated the association between serum 25(OH)D concentration and the risk for hypertension using the Intermountain database found a highly significant association of very low and low baseline serum 25(OH)D concentrations and the prevalence of hypertension at an average of 1.3 years followup (rated C). The Intermountain data were analyzed with 25(OH)D cutoff points of 37.5 and 75 nmol/L. Significant associations were identified for those with serum concentrations

below 75 nmol/L. An assessment of the association between serum 25(OH)D and incident hypertension in 1,211 participants in the Physicians' Health Study (men of average age 57.6) at a mean followup of 15.3 years (maximum 27 years) showed a marginally significant j-shaped association, with men in the lowest two quartiles and in the highest quartile at higher risk for incident hypertension than those in the third quartile (rated A).

The original report identified no relevant RCTs. In a B-rated combined analysis of the Health Professionals Followup Study and the Nurses' Health Study, significantly higher incidence of hypertension at 4 years was found in men and women (mostly within the 51 to 70 year old life stage) with serum 25(OH)D concentrations less than 37.5 nmol/L, compared with those with higher 25(OH)D concentrations. At 8 years, a similar significant association was found for men but not for women.

Blood Pressure

The current study identified 10 new RCTs that assessed the effects of 1 or more dosage levels of vitamin D compared with placebo on blood pressure in adults. Dosages ranged from 125 IU to 5700 IU per day. Followup ranged from 3 months to 1 year. Participants included postmenopausal women; middle-aged U.S. blacks (rated A); overweight young Chinese and Dutch adults; healthy South Asian women residing in the United Kingdom; and healthy young women from Spain. Of the 10 RCTs, no effect of vitamin D supplementation was observed in 7 (5 rated A and 2 rated B); vitamin D significantly decreased systolic blood pressure in 2 studies (both systolic and diastolic in one of the studies) (rated B); and in the final study, systolic blood pressure actually increased slightly in the supplemented group (rated C).

The original report evaluated only RCTs for changes in blood pressure. Three RCTs of vitamin D versus placebo (one rated A, two B) evaluated blood pressure outcomes. The trials used a range of vitamin D dosages (800 IU/d to 120,000 IU every 2 weeks), with or without supplemental calcium in both groups. All trials reported no significant effect on diastolic blood pressure, but the effect upon systolic blood pressure was inconsistent. The three trials found either a net reduction, no change, or a net increase in systolic blood pressure with vitamin D supplementation after 5–8 weeks.

Combined Vitamin D and Calcium

Combined Vitamin D and Calcium and Growth

The current report did not consider growth as an outcome, except for prenatal growth. No new studies were identified. In the original report, one C-rated nonrandomized study from India compared combined vitamin D (1200 IU/d) and calcium (375 mg/d) to no supplementation in women in their third trimester of pregnancy. Infants of women who received supplementation were significantly heavier at birth.

Combined Vitamin D and Calcium and Cardiovascular Events

For the original study, a variety of cardiovascular events after 7 years were evaluated in the WHI trial of combined vitamin D (400 IU/d) and calcium carbonate (1000 mg/d) (CaD) versus placebo in postmenopausal women. This study was rated B. No significant effect was found with combined vitamin D and calcium supplementation on any cardiovascular outcome. However, borderline nonsignificant associations were found for three outcomes, suggesting increased risk

with supplementation for a composite cardiac outcome, invasive cardiac interventions, and transient ischemic attacks. No significant associations were found for a composite cardiac outcome, coronary heart disease death, myocardial infarction, hospitalization for heart failure, angina, stroke or transient ischemic attack, and stroke alone.

The current report identified only one new study that assessed the effects of vitamin D and calcium supplements combined on cardiovascular events: A post hoc analysis of the WHI CaD trial that stratified participants on the basis of personal supplement use before and during the trial found no impact of the study supplements alone (either positive or negative) on risk for cardiovascular events (rated A).

Combined Vitamin D and Calcium and Body Weight

This outcome was not investigated for the current report.

For the original report, no studies evaluated the risk of obesity or overweight. Only RCTs were evaluated for changes in body weight. Two RCTs (rated B and C) were identified that evaluated the effects of combined vitamin D and calcium supplementation on body weight in the setting of either an energy neutral diet or an energy restricted diet. Both used vitamin D 400 IU per day and calcium carbonate (1,000 mg/d or 1,200 mg/d) and were restricted to women. The B-rated WHI trial, after 7 years, found a highly significant (P=0.001), but clinically questionable net difference of -0.13 kg between the supplemented and placebo groups. In a small C-rated trial, after 15 weeks, those overweight women on supplement lost 4 kg and those on placebo lost 3 kg. This difference was not statistically significant.

Combined Vitamin D and Calcium and Cancer

Total Cancer

No new studies were identified for the current report on the association of combined vitamin D and calcium intake with any cancer outcomes. However, as described below, data from the WHI calcium and vitamin D (CaD) trial were reanalyzed.

Two RCTs (rated B and C) **identified for the original report** reported effects of combined vitamin D and calcium supplementation on the risk of total cancer. The RCTs reported inconsistent results. The B-rated WHI trial (vitamin D 400 IU/d and calcium 1,000 mg/d) showed no effects while the B-rated trial (vitamin D 1,000 IU/d and calcium 1,400–1,500 mg/d) reported a significant reduction of total cancer risk. However, baseline serum 25(OH)D concentrations were substantially different between these two trials (42 nmol/L [WHI] versus 72 nmol/L).

Colorectal Cancer

Only the B-rated WHI trial **identified for the original report** evaluated colorectal cancer. It reported no significant reduction in colorectal cancer incidence or mortality with combined vitamin D (400 IU/d) and calcium carbonate (1,000 mg/d) compared with placebo. **A post hoc analysis of the WHI CaD trial identified for the current report that stratified participants by baseline use of personal vitamin D and calcium supplements found no difference in risk for colorectal cancer by previous or additional supplement use.**

Colorectal Polyps

The B-rated WHI trial **identified for the original report** was the only trial of combined vitamin D_3 and calcium supplements to evaluate colorectal polyps. It found no significant effect of supplementation on colorectal polyp incidence. A B-rated subgroup analysis of a secondary prevention trial of adenomatous adenoma reported that people taking calcium supplements (1200 mg/d) who had higher baseline serum 25(OH)D concentrations (>72.6 nmol/L) had significantly lower risk of relapse compared with placebo. In contrast, among people with lower baseline serum 25(OH)D concentrations, there was no significant difference in relapse rates between those taking calcium supplements or placebo (P=0.01 for interaction between calcium supplementation and 25(OH)D concentration).

Breast Cancer

Only the B-rated WHI trial evaluated breast cancer. It reported no significant reduction in breast cancer incidence or mortality with combined vitamin D (400 IU/d) and calcium carbonate (1000 mg/d) compared with placebo. **A post hoc analysis of the WHI CaD trial identified for the current report that stratified participants by baseline use of personal vitamin D and calcium supplements found a trend toward a reduction in risk for breast cancer among women in the intervention group who had not been using personal supplements at baseline.**

Combined Vitamin D and Calcium and Preeclampsia, Hypertension in Pregnancy, and Preterm Birth or Small Infant for Gestational Age

Preeclampsia

No new studies were identified for the current report that assessed this outcome. In the original report, one C-rated RCT found no significant effect of combined vitamin D (1200 IU/d) and calcium (375 mg/d) supplementation on prevention of preeclampsia.

Other Outcomes

No studies evaluated the relationship of vitamin D with or without calcium and pregnancy-related high blood pressure, preterm birth, or small infant for gestational age.

Combined Vitamin D and Calcium and Bone Health

The results reported in this section are based on the Ottawa EPC Evidence Report "Effectiveness and Safety of Vitamin D in Relation to Bone Health" and on our updated literature review of studies published after its completion.

Rickets, Fractures, Falls, or Performance Measures

For the current report, we identified no new studies on the effect of vitamin D and calcium supplementation on rickets that met the inclusion criteria.

The current report identified one new RCT and one reanalysis of the WHI CaD trial that examined the effect of an intervention with vitamin D and calcium on osteoporotic fracture risk among postmenopausal women. The reanalysis of data from the WHI CaD trial compared the effects of the intervention between women who had been using personal vitamin D and/or calcium supplements at baseline. The primary outcome was risk for hip fracture at 5 or more years and secondary outcomes included other fractures. The reanalysis found that among women who were not taking calcium or vitamin D

supplements at baseline, the risk for hip fracture was significantly decreased (no effect was seen among women who had been taking supplements); it found no effect of the intervention on overall fracture risk in women who had been taking supplements or in those who had not (rated A).[2] The second RCT, the OSTPRE study, found no effect of 3 years' supplementation with calcium and vitamin D on risk for total, nonvertebral, distal forearm, upper extremity, or lower extremity fragility fractures among 3,195 postmenopausal women age 65 to 71 years (rated A).

One RCT on middle-age and older Australian men (age 50 to 79) tested the effect of an 18-month intervention of daily vitamin D (800 IU) and calcium (1,000 mg) on measures of muscle function (rated A). No effect was seen on any measure of muscle function, including step test, gait speed, or sway.

We identified one new RCT that assessed effects of supplementation on risk for falling: This study found no effect of the intervention (study rated C).

As described in the original report, the Ottawa EPC report concluded that supplementation with vitamin D (most studies used D_3) plus calcium is effective in reducing fractures in institutionalized populations, but evidence that supplemental vitamin D reduces falls in postmenopausal women and older men is inconsistent.

One study published after the Ottawa EPC report analyzed the performance measure outcomes in a small sample of postmenopausal women from the WHI trial. After 5 years, the study found generally no differences in performance measures between the groups taking vitamin D (400 IU/d) plus calcium (1,000 mg/d) supplementation or placebo. One RCT of premenopausal women (aged 17–35 years) found that vitamin D (800 IU/d) in combination with calcium (2,000 mg/d) supplementation reduced the risk of stress fracture from military training compared with placebo.

Bone Mineral Density or Bone Mineral Content

Of the seven new RCTs identified for this report on the effect of vitamin D and calcium supplementation on bone density or content, two studies were in girls (rated B) or young women (rated A): Both showed positive effects on BMC and BMD, respectively. Four of the RCTs enrolled postmenopausal women (one rated A, two rated B, and one rated C): All showed some positive effects, but the effects differed across the studies in the areas that were positively affected. One intervention that enrolled men showed no effects (rated A). Followup times ranged from 1 to 6 years. Vitamin D supplementation ranged from 200 to 800 IU per day, with calcium ranging from 600 to 1200 mg per day.

As described in the original report, the Ottawa EPC report concluded that overall, there is good evidence that combined vitamin D_3 and calcium supplementation resulted in small increases in BMD of the spine, total body, femoral neck, and total hip. In RCTs among (predominantly) postmenopausal women, vitamin D_3 (<800 IU/d) plus calcium (500 mg/d) supplementation resulted in small increases in BMD of the spine, the total body, femoral neck and total hip.

For this outcome, only RCTs were included for the update literature review. Three new RCTs (two rated B, one C) were identified that evaluated BMD outcomes. Two of the trials showed significant improvement in BMD in postmenopausal women receiving vitamin D_2 (300 IU/d) or D_3 (1,200 IU/d) plus calcium (1,200 mg/d) compared with placebo.

One C-rated RCT evaluated BMC outcomes in healthy girls (aged 10–12 years). Compared with placebo, there was no significant effect of supplementation with vitamin D_3 (200 IU/d) plus calcium (1,000 mg/d) on BMC changes.

Combined Vitamin D and Calcium and All-Cause Mortality

No new studies were identified for the current report that addressed this question. For the original report, an existing systematic review and metaanalysis of 18 RCTs on vitamin D supplementation for mortality was reanalyzed. No additional RCTs were identified. Eleven RCTs (N=44,688) of combined vitamin D (300–800 IU/d) and calcium (500–1,200 mg/d) supplementation met inclusion criteria for our reanalysis. The metaanalysis found no significant relationship between combined supplementation of vitamin D and calcium and all-cause mortality (RR=0.93, 95% CI 0.86, 1.01; random effects model). There is little evidence for between-study heterogeneity in these analyses. Among eight RCTs (N=44,281) in postmenopausal women, there was no significant effect of supplementation on all-cause mortality.

Combined Vitamin D and Calcium and Hypertension and Blood Pressure

No new studies were identified for the current report that addressed this question. For the original report, only the B-rated WHI trial evaluated the risk of developing hypertension. Among the subset of women without hypertension at baseline, at 7 years the trial found the combined supplementation had no effect on incident hypertension. Only RCTs were evaluated for changes in blood pressure. Two trials (one rated B, one C) tested combined vitamin D (400 IU/d) and calcium (1,000 or 1,200 mg/d) and blood pressure. Both found no significant effect of supplementation on blood pressure after 15 weeks or 6.1 years.

How Does Dietary Intake of Vitamin D From Fortified Foods and Vitamin D Supplementation Affect Serum 25(OH)D Concentrations (Arrow 4)?

The results reported in this section are based on the Ottawa EPC Evidence Report "Effectiveness and safety of vitamin D in relation to bone health," on our updated literature review of studies published after its completion, **on new studies identified for the current report, and on a high-quality systematic review published since the original report**.

The current report identified 1 new existing systematic review published since the original report that addressed the question as well as 18 new RCTs that met the inclusion criteria (2 that used fortified foods and the remainder that used supplements). The systematic review, based on 76 RCTs, reported widely varying increases in serum concentrations of 25(OH) for similar doses of vitamin D, with a general increase in serum concentration with supplement administration. Of the RCTs identified for the current report that met the criteria for inclusion in an assessment of dose response, all reported increases in serum 25(OH)D with supplementation; however, the findings varied by age group and health status of participants, baseline serum 25(OH)D concentration, dose, duration, and assay used to assess serum 25(OH)D. Only one study used the National Institute of Standards and Technology vitamin D as a reference standard, and six reported

participating in the Vitamin D External Quality Assessment Scheme. Of 54 RCTs included in the original and the current report, only 4 reported the year the assays were conducted.

As described in the original report, the Ottawa EPC report concluded that there is "good" evidence that dietary intake of vitamin D increases serum 25(OH)D concentrations among adults. Our updated search did not identify new RCTs on dietary intakes of vitamin D from fortified foods.

We graphically evaluated the net changes in serum 25(OH)D concentration against the doses of vitamin D supplementation using data from 26 RCTs with 28 comparisons in adults. Only RCTs of daily vitamin D_3 supplementation (doses ranged from 200 to 5000 IU/d) alone or in combination with calcium supplementation (doses ranged from 500 to 1550 mg/d) that provided sufficient data for the calculations were included. The relationship between increasing doses of vitamin D_3 with increasing net change in 25(OH)D concentration was evident in both adults and children. It was also apparent that the dose-response relationships differ depending on study participants' serum 25(OH)D concentrations (≤40 vs. >40 nmol/L) at baseline, and depending on duration of supplementation (≤3 vs. >3 months).

Stratification of Key Outcomes by Vitamin D Assay Method

In addition to plotting the data for Vitamin D dose-response by the method used to assay serum 25(OH)D (Figure 15), for all outcomes reported in three or more RCTs or seven or more observational studies, we stratified the studies according to the assay method used to assess serum 25(OH)D concentrations (radioimmunoassay, radioreceptor/ligand assay, enzyme-linked immunoadsorption assay, chemiluminescence assay, and HPLC-tandem[a] mass spectrometry). These stratified tables appear in Appendix H of the full report.

Outcomes for Tolerable Upper Intake Levels

We included only clinical outcomes of tolerable upper intake levels, such as all-cause mortality, cancer (incidence and mortality), soft tissue calcification, renal outcomes, and adverse events reported in RCTs. Results of all-cause mortality and cancer have been described in previous sections.

Renal Outcomes

As described in the original report, the WHI trial (vitamin D_3 400 IU in combination with 1,000 mg calcium carbonate vs. placebo) found an increase in the risk of renal stones. No other study was identified that evaluated the effect of vitamin D, calcium, or combined vitamin D and calcium on other renal outcomes.

For the current report, two new studies assessed the occurrence of nephrolithiasis among participants in RCTs that administered approximately 1,100 and 2,000 IU per day supplemental vitamin D without calcium. No incidents of nephrolithiasis were reported in either study.

[a] HPLC is high pressure liquid chromatography.

Adverse Events Reported in RCTs

The **original report noted that** reporting of adverse events in RCTs was generally inadequate, and most trials were not adequately powered to detect adverse events. Among the 63 RCTs included in the original report, 47 did not report information on adverse events.

Among 18 new RCTs included in the current study, most did not include any information on adverse events. One study, which administered 2000 or 4000 IU per day to women during the third trimester of pregnancy reported no adverse events. Three studies reported on only one specific outcome, hypercalcemia/serum calcium, or reported on this outcome and stated that no other adverse events were reported. Supplementation ranged from 400 to 5000 IU per day in these studies; only 1 case of hypercalcemia was reported across all 4 of the studies, in a trial that administered 1000 IU per day plus 1000 mg calcium. Five other studies that assessed hypercalcemia also reported no cases.

Five new studies reported on gastrointestinal symptoms, of which only one included supplemental calcium. Two new studies reported on serious adverse events, including one death, cancer diagnoses, and acute surgeries, which were more prevalent in the placebo group and thus could not have been related to the use of vitamin D.

In the original report, 5 RCTs (in 6 publications) that enrolled a total of 444 subjects reported no adverse events during the trial periods. Eleven RCTs reported at least one adverse event. Excessive gas, bloating, and gastrointestinal discomforts were reported to be associated with calcium supplementation (doses ranged from 600 to 1000 mg/d). Other RCTs of vitamin D (doses ranged from 400 to 5,714 IU/d vitamin D_3 or ranged from 5000 to 10,000 IU/d vitamin D_2) and/or calcium supplementations (doses ranged from 200 to 1,500 mg/d) reported few cases of gastrointestinal disruption (such as constipation, diarrhea, or upset stomach), musculoskeletal soreness, primary hyperparathyroidism, hypercalcemia, and renal calculi. However, these adverse events may or may not be associated with vitamin D and/or calcium supplementation in this study.

Summation

The **original** systematic review identified 165 primary study articles and 11 systematic reviews (which incorporated over 200 additional primary articles) that met the eligibility criteria established by the Technical Expert Panel. **The current study identified 154 new articles (reporting 156 studies) and two systematic reviews that met the eligibility criteria.** Despite the relatively large number of studies included, with the following few exceptions, it is difficult to make any substantive statements on the basis of the available evidence concerning the association of either serum 25(OH)D concentration, vitamin D supplementation, calcium intake, or the combination of both nutrients, with the various health outcomes because most of the findings were inconsistent.

In general, **the original report found that** among RCTs of hypertensive adults, calcium supplementation (400–2,000 mg/d) lowered systolic, but not diastolic, blood pressure by a small but statistically significant amount (2–4 mm Hg). **The current report did not address calcium supplementation alone.**

For **adult** body weight, despite a wide range of calcium intakes (from supplements or from dairy and nondairy sources) across the calcium trials, the RCTs **identified for the original report** were fairly consistent in finding no significant effect of increased calcium intake on body weight. **The current report addressed body weight only in infants and did not address the effects of calcium. Effects of vitamin D interventions on birth weight were inconclusive.**

For growth, a metaanalysis of 17 RCTs **identified for the original report** did not find a significant effect on weight and height gain attributable to calcium supplement in children ranged from 3 to 18 years of age. **The current report did not address pediatric weight or height gain or the effects of calcium alone.**

For **intermediate indices of** bone health, one well-conducted systematic review of RCTs **identified for the original report** found that vitamin D_3 (up to 800 IU/d) plus calcium (approximately 500 mg/d) supplementation resulted in small increases in BMD of the spine, total body, femoral neck, and total hip in populations consisting predominantly of women in late menopause. **Of the studies identified for the current report, one of seven RCTs of vitamin D supplementation alone and six of seven RCTs of vitamin D plus calcium found increases in BMC/BMD: The study of vitamin D alone that reported a positive effect enrolled infants, whereas the studies of vitamin D and calcium primarily enrolled postmenopausal women; the study that reported no effect of administering both vitamin D and calcium enrolled only men. Thus, the findings from the 2009 report with respect to both vitamin D alone and in combination with calcium relevant to intermediate indices of bone health remain unchanged with the incorporation of newer, relevant data. Findings on clinical outcomes are reported above.**

For clinical outcomes of bone health (fracture risk), a post-hoc analysis of the WHI CaD 7-year data that stratified participants by use of personal vitamin D and calcium supplements at baseline found that among women not taking supplements at baseline, the intervention significantly reduced the risk for hip fracture.

For breast cancer, subgroup analyses in four cohort studies **identified for the original report** consistently found that calcium intake in the range of 780 to 1,750 mg/d in premenopausal women was associated with a decreased risk for breast cancer. In contrast, cohort studies of postmenopausal women are consistent in showing no association of calcium intake with the risk of breast cancer. **Studies of calcium alone were not included in the updated report.**

For prostate cancer, three of four cohort studies **identified for the original report** found significant associations between higher calcium intake (>1,500 or >2,000 mg/day) and increased risk of prostate cancer, compared with men consuming lower amount of calcium (500–1,000 mg/day). **Studies of calcium alone were not included in the updated report.**

For cardiovascular events, a cohort study and a nested case-control study **identified for the original report** found associations between lower serum 25(OH)D concentrations (less than either about 50 or 75 nmol/L) and increased risk of total cardiovascular events; however, a RCT found no effect of supplementation, and studies of specific cardiovascular events were too sparse to reach conclusions. **For the current report, studies assessing associations between cardiovascular events and serum 25(OH)D concentrations also reported inconsistent results. Thus, the findings from the 2009 report relative to vitamin D remain unchanged with the incorporation of newer, relevant data. One high-quality systematic review that included some of the studies reviewed in the original report and some in the current report found a significant association between lower serum 25(OH)D concentrations and increased risk for total cardiovascular disease and coronary heart disease risks.**

Taken together, six cohort studies of calcium intake suggest that in populations at relatively increased risk of stroke and with relatively low dietary calcium intake (i.e., in East Asia), lower levels of calcium intake under about 700 mg per day are associated with higher risk of stroke. This association, however, was not replicated in Europe or the United States, and one Finnish

study found a possible association of increased risk of stroke in men with calcium intakes above 1,000 mg. **Again, studies of calcium alone were not included in the current report.**

Studies on the association between either serum 25(OH)D concentration or calcium intake and other forms of cancer (colorectal, pancreas, prostate, all-cause); incidence of hypertension or specific cardiovascular disease events; immunologic disorders; and pregnancy-related outcomes including preeclampsia were either few in number or reported inconsistent findings. Too few studies of combined vitamin D and calcium supplementation have been conducted to allow adequate conclusions about its possible effects on health. The WHI trial was commonly the only evidence available for a given outcome.

For the current report, we abstracted the methods used to assay serum 25(OH)D for all RCTs included in the assessment of dose-response, as well as the RCTs included in the original report and plotted dose response according to assay method. Although most studies employed radioimmunoassays, some relied on other immunoassay methods, receptor binding assays, and HPLC/tandem mass spectrometry. To characterize the assay methods more completely, we also noted the country and year in which the assay was performed, when reported, and any information provided on standardization; however, very few studies reported the year assays were conducted or how assays were standardized. Combined with the evidence regarding the significant effect of season of blood draw on serum 25(OH)D concentrations, this lack of information on year of assay renders comparing or combining outcomes challenging, even when the same type of assay was used.

As demonstrated by the findings of a number of trials and post hoc analyses identified for the current report, adherence to interventions in trials also remains a barrier to interpretation of study findings and assessing the true effects of supplementation on health outcomes.

Table A summarizes the findings of the 2009 and current reports by study design and compares the findings across reports. “None identified” indicates that no studies were identified for that outcome and study design. “None included” indicates that studies for that outcome or of that design were excluded from the reports. For observational studies, “inverse association” refers to an association between lower serum 25(OH)D concentrations and a higher risk for the outcome of interest; “association” or “positive association” refers to an association between higher serum 25(OH)D concentration and a higher risk for the outcome.

Table A. Findings of the original report compared with the current report

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Bone Health Vitamin D						
Rickets	None identified	None identified	Conclusions based on 2006 Ottawa EPC report showed strong effect	None identified	None identified	No new studies to compare
BMD/BMC	(3 RCTs) No effects of vitamin D supplementation on BMC or BMD	None included	The Ottawa EPC report concluded that observational studies suggested a correlation between higher serum 25(OH)D concentrations and larger values of BMC indices for older children and adolescents	(8 RCTs) 1 RCT in infants showed a trend toward a positive effect on BMC; 1 RCT in postmenopausal women showed reduced loss of hip BMD but not spinal; 6 RCTs showed no effect	None included	Both 2009 and newer studies had mixed results
Fracture	(3 RCTs) no effect of vitamin D on total fracture risk	None identified	Conclusions based on 2006 Ottawa EPC report were mixed	None identified	(8 observational studies) 3 studies of hip fracture showed mixed results; 1 showed a significant inverse association. Two studies of nonvertebral fracture showed no association; 1 showed a significant association. Two studies of total fragility fracture showed mixed results.	Both 2009 and newer studies had mixed results

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Muscle strength/ falls	None included	None included	Conclusions based on 2006 Ottawa EPC report were mixed	(2 RCTs on fall risk in elderly) 1 reported no effect; 1 reported effects only in subgroups) (2 RCTs on muscle strength) both showed positive effects but one showed effects only in those with lower serum 25(OH)D	(1 prospective cohort on falls) inverse association of 25(OH)D and falls risk (4 prospective cohort studies on muscle strength) ¾ showed inverse association of 25(OH)D with muscle strength	Both original and newer studies had mixed results
Bone Health Vitamin D+Ca						
Rickets	None identified	None identified		None identified	None identified	
BMD/BMC	(3 RCTs) 1 RCT in healthy girls showed no effects on BMC; 2 RCTs in postmenopausal women showed positive effects on BMD	None included	Ottawa EPC report concluded that overall, there is good evidence that vitamin D+Ca resulted in small increases in BMD of the spine, total body, femoral neck, and total hip	(7 RCTs) 2 RCTs in girls and young women showed positive effects; 4 RCTs in post- menopausal women had mixed effects; 1 RCT in men showed no effects	None included	Both original and newer studies had mixed results

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Fracture	(1 RCT) Vitamin D+Ca reduced risk of stress fracture among premenopausal women	None identified	Ottawa EPC report concluded that supplementation with vitamin D +calcium is effective in reducing fractures in institutionalized populations	(1 RCT and 1 post-hoc analysis, both rated A) Post-hoc analysis of year-7 WHI data showed significantly decreased risk for hip fracture (but not overall fracture) among women who did not use personal supplements at baseline; 3-year study of postmenopausal women found no effect on fracture at any site	None identified	General agreement among original Ottawa EPC report, 2009 report, and current report that vitamin D+Ca reduces risk for some fractures but not consistent across fracture types or populations. Post-hoc analysis of WHI data demonstrates need to consider baseline supplement use.
Muscle strength/ falls	(1 RCT) 5-year analysis of WHI subsample found no effect on performance	None included	Ottawa EPC report found evidence that supplemental vitamin D reduces falls in postmenopausal women and effect for older men is inconsistent	(1 RCT on muscle strength/1 RCT on falls) no effects of vitamin D+Ca on muscle strength or fall risk	None identified	2009 report consistent with current report that vitamin D+Ca supplementation does not affect risk for falls or muscle strength but too few studies to draw firm conclusions

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Pregnancy-Related Outcomes Vitamin D						
Birth weight/ length (infancy)	(7 RCTs) 2 out of 7 studies (from same center) reported significant effect of supplement on birth weight; 5 reported no effects	(2 prospective cohorts) no effects	Diverse populations and methodological approaches precluded conclusions	(5 RCTs) 1 out of 5 reported significant effect of supplement intake on birth weight and length; remaining 4: no effect	(2 prospective cohorts) half observed association of 2nd trimester maternal serum 25(OH)D with birth weight	Only 1 C-rated RCT observed an effect of vitamin D; compliance was a challenge in several RCTs
Small-for gestational age (SGA)	No studies identified	No studies identified	NA	No studies identified	(2 prospective cohort studies) 1 found an inverse association of serum 25(OH)D with risk for SGA; the other found a U-shaped association	Differences in observations between studies
Preterm birth	No studies identified	No studies identified	NA	No studies identified	(1 prospective cohort study and 1 nested case-control) the prospective cohort observed an inverse association with risk, the nested case-control observed no association	Differences in observations among studies

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Preeclampsia	No RCTs identified	(1 nested case-control) study observed an association between serum 25(OH)D <37.5 nmol/L and increased risk for preeclampsia	Studies too small in number to reach conclusions	(2 RCTs (pooled in one article)) vitamin D supplementation (4000IU/d but not 2000IU) reduced the risk for preeclampsia	(7 observational studies (5 nested case-control and 2 prospective cohort)): 5 of 7 studies observed an association between serum 25(OH)D<50nmol/L and increased risk for preeclampsia	Newer studies suggest possible effect of serum 25(OH)D concentration or vitamin D supplementation on reducing risk for preeclampsia
Pregnancy-Related Outcomes Vitamin D + Ca						
Birth weight/length (infancy)	(1 C-rated nonrandomized trial) study found significant effect of vitamin D+Ca supplementation on birth weight	No studies identified	Too few studies to assess findings	No new studies identified	No new studies identified	No studies for which to assess findings
SGA	No studies identified	No studies identified		No new studies identified	No new studies identified	No studies for which to assess findings
Preterm birth	No studies identified	No studies identified		No new studies identified	No new studies identified	No studies for which to assess findings
Preeclampsia	(1 C-rated RCT) Study found no significant effect of combined vitamin D (1200 IU/d) and calcium (375 mg/d) on prevention of preeclampsia	No studies identified	Too few studies to assess findings	No new studies identified	No new studies identified	No studies for which to assess findings

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
All-Cause Mortality						
All-cause mortality Vitamin D	(1 RCT and reanalysis of existing SR) vitamin D supplementation had no significant effect	(4 cohort studies): 3 reported no association; 1 reported a trend toward an inverse association	No relationship of vitamin D with all-cause mortality	None identified	(25 observational studies) 7 reported no association; 16 reported an inverse association; 2 reported a U-shaped association	Both the 2009 and the current report suggest no relationship of vitamin D with all-cause mortality
All-cause mortality Vitamin D+Ca	(reanalysis of existing SR) vitamin D+Ca supplementation had no significant effect	None identified	No relationship of vitamin D+Ca and all-cause mortality	None identified	None identified	No literature on vitamin D+Ca and all-cause mortality
CVD Vitamin D						
Hypertension	None identified	(2 observational studies) 2 large prospective cohort studies observed a significant inverse association of serum 25(OH)D with risk for hypertension	Too few studies to draw conclusions	None identified	(2 observational studies) 1 C-rated prospective cohort study observed an inverse association between serum 25(OH)D and risk for hypertension; 1 A-rated cohort study observed a j-shaped association with risk for hypertension	Relative agreement between 2009 report findings and current report except for observed j-shaped association between serum 25(OH)D and hypertension risk

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Blood pressure	(3 RCTs) 3 trials reported no effect of vitamin D on diastolic blood pressure, but diastolic pressure was decreased in 1 study, unchanged in 1, and increased in 1			(10 RCTs) 7 reported no effect, vitamin D decreased blood pressure in 2 studies, and vitamin D increased systolic blood pressure in 1	None included	2009 report and current report agree that effects of vitamin D supplementation on blood pressure are inconsistent, based on small numbers of studies
CVD events	(1 RCT) No effect of vitamin D supplementation on risk for CV events in elderly	(4 cohort studies) 2 studies reported a significant inverse association between serum 25(OH)D and total CV events; 2 studies reported no associations	Mixed effects reported	None identified	(1 SR of prospective studies; 7 new studies) SR found significant inverse association of serum 25(OH)D and CV events; new cohort studies found mixed effects	Associations of serum 25(OH)D with CVD events observed in some cohort studies but not all and not supported by RCTs
CVD mortality	(1 RCT) No effect of vitamin D supplementation on risk for CV death in elderly	None included	Too few studies to draw conclusions	None identified	(7 cohort studies, 1 nested case-control) Increased risk for cardiovascular death for those with the lowest serum 25(OH)D concentrations compared with the highest	Mixed findings between 1 RCT in 2009 report and 8 observational studies identified for current report

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
CVD Vitamin D+Ca						
Hypertension	(1 RCT) The WHI reported no effect of vitamin D+Ca supplementation on hypertension risk	None identified	No effects reported; small number of trials	None identified	None identified	2009 report and current report identified no effects
Blood pressure	(2 RCTs) No effect of supplementation seen on blood pressure at short or long followup times	None included	No effects reported; small number of trials	None identified	None included	2009 report and current report identified no effects
CVD events	(1 RCT) WHI CaD Trial 7-year followup found no effect on any CV outcome, but a trend toward increased risk for a composite cardiovascular outcome with supplementation	None included	No significant effects of Vitamin D+Ca but trend toward increasing risk of CV events with supplementation	(1 post-hoc analysis of the WHI trial) no effect of study supplements (400IU vitamin D_3 and 1000mg Ca) alone on risk for CV events at >5 years followup	None identified	Post-hoc reanalysis of WHI CaD outcomes by use of personal supplements at baseline finds no effect of study intervention on risk for CVD

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Cancer Vitamin D						
Total cancer/ cancer mortality	(2 RCTs) no effect of vitamin D supplementation on risk for cancer mortality	(1 cohort study) analysis of NHANES III found no association between 25(OH)D status and risk for cancer mortality		No new RCTs identified	(2 cohort studies assessed association with cancer incidence) no association of 25(OH)D and total cancer incidence (10 cohort studies and 1 nested case-control assessed association with total cancer mortality) 5 cohort studies saw no association; 3 cohorts and the nested case-control observed a trend toward an inverse association; 1 observed a trend toward a positive association; 1 observed a U-shaped association	Totality of studies suggest no or complicated association of 25(OH)D status with cancer mortality

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Prostate cancer	No studies identified	(12 nested case-control studies) 8 studies found no association between serum 25(OH)D concentrations and prostate cancer risk; 1 study found a significant inverse association between lower baseline serum 25(OH)D concentrations (<30 compared with >55 nmol/L) and higher risk (rated C); another C-rated study observed a U-shaped association (C-rated)	Observational studies only; mixed findings on associations	No studies identified	(7 observational studies) 4 nested case-control studies and 1 cohort found no association of serum 25(OH)D with risk for prostate cancer; 2 nested case-controls observed a trend toward increasing risk with higher serum 25(OH)D concentrations	2009 and current report find observational studies only, with mixed findings on associations

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Breast cancer	No studies identified	(2 observational studies) 2 nested case-controls observed no association of serum 25(OH) status with risk for breast cancer in 7–12 years followup	Two observational studies suggest no association	(1 RCT on breast density) vitamin D intake greater than 400IU/d decreased mammographic density	(8 observational studies) 2 cohort and 4 nested case-control studies found no association; 2 nested case-control studies found increasing risk of breast cancer with decreasing 25(OH)D concentrations	2009 and current report find observational studies only, with mixed findings on associations
Colorectal cancer(CRC)	(1 RCT) no effect of supplements over 5 years followup	(8 observational studies) 2 nested case-control studies and 1 cohort study found inverse associations between 25(OH)D concentrations and risk for CRC; 5 nested case-control studies found no association	Observational studies report mixed associations and RCT shows no effect	No studies identified	(4 observational studies) 3 nested case-control studies identified a trend toward an inverse association of 25(OH)D and CRC risk; 1 nested case-control found no association	2009 and current report identify mixed findings
Pancreatic cancer	No studies identified	(2 observational studies) risk for pancreatic cancer increased with increasing serum 25(OH)D concentrations	Two few studies to draw conclusions	No studies identified	(8 nested case-controls pooled) risk for pancreatic cancer increased among those with 25(OH)D>100 nmol/L compared with <25nmol/L	Observational studies in 2009 and current reports suggest increasing risk for pancreatic cancer with increasing serum 25(OH)D

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Cancer Vitamin D+Ca						
Total cancer mortality	No studies identified	No studies identified		No studies identified	No studies identified	No studies on which to base comparison or conclusions
Prostate cancer	No studies identified	No studies identified		No studies identified	No studies identified	No studies on which to base comparison or conclusions
Breast cancer	(WHI CaD Trial) WHI reported no significant effect of supplements on the risk for breast cancer	No studies identified		(WHI CaD post-hoc analysis) assessment of breast cancer risk among trial participants stratified by use of personal supplements at baseline reported a trend toward decreasing risk among women who did not use personal supplements	No studies identified	Too few studies to draw conclusions
Colorectal cancer (CRC)	(WHI CaD Trial) WHI reported no significant effect of supplements on the risk for CRC	No studies identified	Too few studies to draw conclusions about supplementation	(WHI CaD post-hoc analysis) assessment of CRC risk among trial participants stratified by use of personal supplements at baseline reported no difference in risk between personal supplement users and those who did not use personal supplements	No studies identified	Too few studies to draw conclusions
Pancreatic cancer	No studies identified	No studies identified		No studies identified	No studies identified	

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Immune Function Vitamin D						
Infectious illnesses	No studies identified	(2 observational studies) NHANES III found no significant association between serum 25(OH)D concentrations and infectious disease mortality		(4 RCTs) 4 RCTs of infants and adults reported no effects	(9 observational studies) 3 cohort studies observed an inverse association of cord blood 25(OH)D and risk for infections at 3–6 months; two cohort studies observed inverse associations among school-age children; 3 cohort studies of adults observed similar associations with various infectious illnesses	Number of studies in 2009 report too small to assess association of serum 25(OH)D with risk for infection; current report identified RCTs and observational studies, but no consistent effects or associations emerged
Autoimmune disorders	No studies identified	No studies identified	No studies on which to base conclusions	(1 RCT) a subgroup analysis of WHI CaD participants found no effect of supplementation on risk for rheumatoid arthritis	(4 observational studies) 3 nested case-control studies and 1 cohort study reported mixed associations of serum 25(OH)D concentrations with risk for type 1 diabetes; 1 study reported mixed associations of serum 25(OH)D with risk for multiple sclerosis	No studies in 2009 report on association of serum 25(OH)D with risk for autoimmune diseases; current report identified 1 RCT and observational studies, but no consistent effects or associations emerged

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Asthma, Wheeze, Atopy		(1 observational study) a cohort study suggested an association of maternal 25(OH)D concentration and increased risk for eczema in their children but did not assess children's serum 25(OH)D	Too few studies on which to base conclusions	(1 RCT) no effect of prenatal supplementation on risk for wheeze, atopy, or eczema	(5 observational studies) mixed associations seen in cohorts of children between serum 25(OH)D status and risk for atopy, eczema, wheeze, and asthma	Number of studies in 2009 report too small to assess association of serum 25(OH)D with risk for asthma, atopy, or wheeze; current report identified 1 RCT and 5 observational studies, but no consistent effects or associations emerged
Immune Function Vitamin D+Ca						
	No studies identified	No studies identified		No new studies identified	No new studies identified	No studies identified in 2009 or current report on which to base conclusions
Adverse events						
Nephro-lithiasis	(WHI CaD Trial) trial reported increased risk for nephrolithiasis among supplement users			(2 RCTs) no incidents of nephrolithiasis were reported in studies that administered 1100 and 2000IU/d vitamin D		Observation of increased risk for nephrolithiasis in original WHI study; very small number of RCTs identified for current report did not support this finding

Table A. Findings of the original report compared with the current report (continued)

Outcome	2009 Report (Number of RCTs) General Finding(s)	2009 Report (Number of Observational Studies) General Findings	2009 Report Comments	2014 Report (Number of RCTs) General Finding(s)	2014 Report (Number of Observational studies) General Findings	2014 Report Comments
Other Adverse Events	47 of 63 RCTs included no information on adverse events; no serious AEs were reported			41 of 55 RCTs included no information on adverse events; 1 RCT reported that no adverse events were reported; of 9 studies that assessed hypercalcemia, 1 RCT that administered 1000IU vitamin D and 1000mg Ca reported1 case		Few studies in the 2009 or the current report reported AEs; consistent finding of new serious AEs
Dose-Response for Vitamin D	(26 RCTs) serum 25(OH)D increased with increasing dosages, but trajectories varied widely by age group, baseline serum 25(OH)D, and duration	Not included		(1 systematic review and 19 RCTs of vitamin D_3 with or without calcium) serum 25(OH)D increased with increasing dosages but trajectories varied widely by age group, baseline serum 25(OH)D, duration, and assay. Too few new studies included Ca to assess effect.	Not included	Observations based on new studies agree with those of 2009 report; current report also stratified dose-response by assay type. Patterns appear to differ slightly but too few studies to ascertain.

Abbreviations: 25(OH)D = 25-hydroxyvitamin D; AEs = Adverse Events; BMD = Bone mineral density; BMC = Bone-mineral content; Ca = Calcium; CaD = Calcium/Vitamin D; CRC = Colorectal Cancer; CVD = Cardiovascular Disease; EPC = Evidence-based Practice Center; IU = International Unit; NHANES III = National Health and Nutrition Examination Survey; RCT = Randomized controlled trial; SGA = Small for gestational age; WHI = Women's Health Initiative

Introduction

Background

This systematic review of the literature constitutes an update of a systematic review that was conducted in 2009. This section describes the background of the original review and this update.

The Food and Nutrition Board of the Institute of Medicine (IOM), with funding from agencies and departments of the United States and Canadian Governments, recently completed their 10-year development of nutrient reference values entitled Dietary Reference Intakes (DRI).[3] In September, 2007, the IOM held a conference to examine the lessons learned and future challenges from the process used to develop the DRI values.[4] One improvement identified at that meeting for DRI updating was the use of systematic reviews to enhance the transparency and rigor of the literature review process that is a necessary component in the deliberations of DRI committees. To assess the feasibility of implementing this approach in the DRI updating process, the Office of Dietary Supplements (ODS) of the National Institutes of Health (NIH) through the Agency for Healthcare Research and Quality (AHRQ) requested the Tufts Medical Center Evidence-based Practice Center (Tufts-EPC) perform an exercise to identify the issues and challenges of conducing systematic reviews as a component of the process used to support the development and updating of DRI values. The Tufts-EPC assembled a group of nutrition experts from academic institutions and federal government agencies, led participants in teleconferences and meetings, and conducted exercises in formulating questions that would be amenable to a systematic review of the scientific literature and abstract screening.[5] One of the intents of this exercise was to identify limitations, challenges, and unanticipated issues that IOM committees may face prior to actually initiating the use of systematic reviews as a routine part of the DRI process.

Following these activities, a working group of United States and Canadian Government scientists convened to determine whether the scientific literature was sufficient to justify a new review of the vitamin D DRI. To address this issue, in May and September of 2007, two conferences were held on the topic of vitamin D and health.[6] As a result of these conferences in March of 2008, the IOM convened a working group of United States and Canadian Government scientists to determine whether significant new and relevant scientific evidence had become available since the 1997 IOM publication of vitamin D DRI to justify initiating a formal review and potential revision of the values.[7] The working group reviewed the proceedings of the two conferences and the results from a systematic review commissioned by the ODS on the effectiveness and safety of vitamin D in relation to bone health conducted by the University of Ottawa EPC (Ottawa-EPC).[8] They concluded that there was sufficient new data on bone health for several of the life stage groups, on potential adverse effects, and on dose-response relationships between intakes and circulating 25-hydroxyvitamin D [25(OH)D] concentrations, and between 25(OH)D concentrations and several health outcomes to warrant a formal review and potential revision of the values.[7] As a result, the NIH/ODS, Public Health Agency of Canada, Health Canada and FDA commissioned the Tufts-EPC to update the Ottawa-EPC report, and systematically review the data related to vitamin D and calcium with respect to a broader spectrum of health outcomes. **The result was the original report on which this current update report is based.**[9]

That original report formed a central portion of the evidence base the IOM committee to Review Dietary Reference Intakes for Vitamin D and Calcium of the Food and Nutrition considered in reviewing the 1997 DRI values for their 2011 update.

In 2013, in preparation for a project the National Institutes of Health Office of Dietary Supplements (NIH/ODS) was undertaking related to evidence-based decision-making for vitamin D in primary care, based on the updated DRI report, the ODS and AHRQ requested an update to the 2009 systematic review that will incorporate the findings of studies on vitamin D and vitamin D administered in conjunction with calcium that have been conducted since the release of the 2009 review. The aim of this update report was to assess many of the outcomes assessed in the original 2009 report, with the exception of outcomes pertaining to body weight and composition and postnatal growth. In addition, the current report did not update the findings on calcium supplementation and status alone, but limited itself to trials of supplementation with vitamin D with or without calcium and to observational studies on serum 25(OH)D concentrations.

This update was requested by the sponsor in anticipation of a conference focused on the evaluation of evidence related to vitamin D and health outcomes, but the update can also be helpful to other stakeholders. The sponsor's interest was to determine whether the inclusion of newer relevant data that became available during the time period following the close of the 2009 review would alter or continue to support the conclusions of the 2009 report. The sponsor's interest did not include the topic area of calcium alone or of growth and body weight as they relate to vitamin D, so for reasons of cost these components of the original report were not included in this review.

Since the analysis for the original report was conducted, evidence has been growing regarding the lack of comparability of results among the various methods for assaying serum 25(OH). Assessing the body of evidence on the outcomes of vitamin D interventions and exposures requires an understanding of how the assay methods compare and the limitations inherent in cross-comparisons. Therefore, for any newly included studies on the effect of vitamin D supplementation on serum 25(OH)D concentrations as well as the studies included in the original report, this update report also provides the details of the vitamin D serum assay methodology, to permit a comparison by assay method.

The text of the original 2009 report has been preserved in its entirety; however, text and tables that report outcomes of calcium supplementation only have been omitted. Here and in the remainder of the report, updated findings are presented in boldface type. The protocol for the update report was posted on the AHRQ website for public comment which can be found at http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1529.

Sources, Metabolism and Functions of Vitamin D

Vitamin D was classified as a vitamin in the early 20th century and in the second half of the 20th century as a prohormone ("conditional" vitamin).[10,11] There are two forms of vitamin D: vitamin D_3 (cholecalciferol), which is produced from the conversion of 7-dehydrocholesterol in the epidermis and dermis in humans, and vitamin D_2 (ergocalciferol) which is produced in mushrooms and yeast. The chemical difference between vitamin D_2 and D_3 is in the side chain; in contrast to vitamin D_3, vitamin D_2 has a double bond between carbons 22 and 23 and a methyl group on carbon 24.

The major source of vitamin D for humans is exposure to sunlight. The efficiency of the conversion of 7-dehydrocholesterol to vitamin D_3 is dependent on time of day, season of the year, latitude, skin color, and age. There is little vitamin D that occurs naturally in the food supply. The major naturally occurring food sources include fatty fish, beef liver, and egg yolk. In the U.S. and Canada, the major dietary source of dietary vitamin D is fortified foods, including cow's milk and, depending on country, other fortified foods and dietary supplements. These sources cannot be relied on in countries other than the U.S. and Canada. Dietary vitamin D is absorbed from the intestine and circulates in plasma bound to a vitamin D binding protein.
In its native form, vitamin D is not biologically active; the active form is $1,25(OH)_2D$. The conversion of vitamin D to $1,25(OH)_2D$ requires two hydroxylations in tandem. Vitamin D is first hydroxylated by the liver to form 25(OH)D, which is then hydroxylated by the kidney to form $1,25(OH)_2D$. 25(OH)D has low biological activity, but it is the major form of vitamin D that circulates in the blood stream. Serum 25(OH)D concentrations are generally thought to reflect nutritional status.[7,8] When adequate amounts of vitamin D are available, the kidney, the major site of $1,25(OH)_2D$ production, converts some of the 25(OH)D to alternate hydroxylated metabolites, which have low biological activity (e.g., $24,25(OH)_2D$ or $1,24,25(OH)_3D$). Renal synthesis of $1,25(OH)_2D$ is tightly regulated by plasma parathyroid hormone (PTH), together with serum calcium and phosphorus concentrations. Additional tissues that express the enzyme that catalyzes the conversion of 25(OH)D to $1,25(OH)_2D$, 25-hydroxyvitamin D3-1-α-hydroxylase, include colon, prostate, mammary gland, macrophages, antigen-presenting cells, osteoblasts, and keratinocytes.[12]

Vitamin D has both genomic and nongenomic functions. For the genomic functions, $1,25(OH)_2D$ interacts with nuclear vitamin D receptors to influence gene transcription. Nuclear receptors for $1,25(OH)_2D$ have been identified in over 30 cell types, including bone, intestine, kidney, lung, muscle, and skin. For the nongenomic functions, $1,25(OH)_2D$ acts like a steroid hormone, working through activation of signal transduction pathways linked to vitamin D receptors on cell membranes. Major sites of action include intestine, bone, parathyroid, liver, and pancreatic beta cells. Biological actions include increases in intestinal calcium absorption, transcellular calcium flux, and opening gated calcium channels, allowing calcium uptake into cells such as osteoblasts and skeletal muscle.

One of the major biological functions of vitamin D is to maintain calcium homeostasis, which impacts on cellular metabolic processes and neuromuscular functions. Vitamin D affects intestinal calcium absorption by increasing the expression of the epithelial calcium channel protein, which in turn enhances the transport of calcium through the cytosol and across the basolateral membrane of the enterocyte. Vitamin D also facilitates the absorption of intestinal phosphate. $1,25(OH)_2D$ indirectly affects bone mineralization by maintaining plasma calcium and phosphorus concentrations, and subsequently extracellular calcium and phosphorus concentrations at the supersaturating range necessary for mineralization. $1,25(OH)_2D$, in concert with PTH, also causes demineralization of bone when calcium concentrations fall, to maintain plasma concentrations within a narrow range. It has yet to be determined whether $1,25(OH)_2D$ directly influences bone mineralization.

In addition to intestine and bone, a wide range of other tissues and cells are influenced by vitamin D. Five biological systems have vitamin D receptors and are responsive to $1,25(OH)_2D$, as summarized in Figure 1.[13] These systems include immune, pancreas, cardiovascular, muscle, and brain, and control of cell cycle. The biological effects of $1,25(OH)_2D$ are diverse. For example, $1,25(OH)_2D$ inhibits PTH secretion and promotes insulin secretion, inhibits adaptive

immunity and promotes innate immunity, and inhibits cell proliferation and stimulates their differentiation.[14] A number of recent reviews have appeared on these topics.[13-21]

Figure 1. Summary of the vitamin D endocrine system [updated figure for the current report]

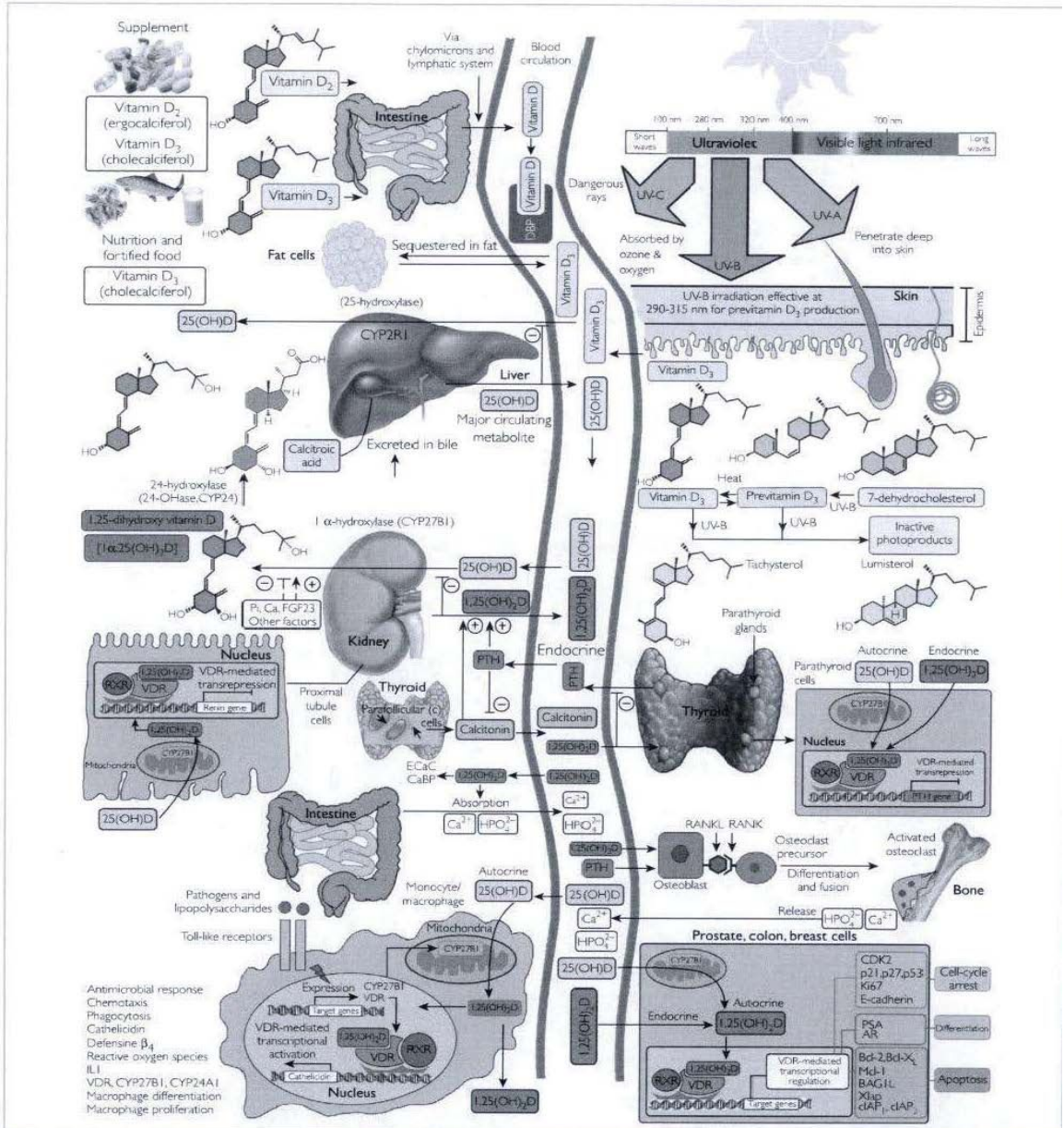


FIGURE 1. Schematic representation of the synthesis and metabolism of vitamin D for skeletal and nonskeletal function. 1-OHase = 25-hydroxyvitamin D-1α-hydroxylase; 24-OHase = 25-hydroxyvitamin D-24-hydroxylase; 25(OH)D = 25-hydroxyvitamin D; $1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; CaBP = calcium-binding protein; CYP27B1, Cytochrome P450-27B1; DBP = vitamin D–binding protein; ECaC = epithelial calcium channel; FGF-23 = fibroblast growth factor-23; PTH = parathyroid hormone; RANK = receptor activator of the NF-kB; RANKL = receptor activator of the NF-kB ligand; RXR = retinoic acid receptor; TLR2/1 = Toll-like receptor 2/1; VDR = vitamin D receptor; vitamin D = vitamin D_2 or vitamin D_3. Copyright Holick 2013, reproduced with permission.

Reprinted from Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. Mayo Clinic Proceedings. 2013 Jul;88(7):720-55. PMID: 23790560 with permission from Elsevier.[21]

Sources, Metabolism, and Functions of Calcium

The major source of dietary calcium in the North American diet, but not necessarily other countries, is dairy products (about 70%). Additional sources include commercial white bread made with calcium sulfate, foods made with milk products, leafy greens, canned fish, and calcium fortified foods. Oxalic acid impedes the absorption of calcium from many plant foods. Intestinal calcium absorption is regulated by two processes. One route of intestinal calcium absorption is dependent on $1,25(OH)_2D$. This process occurs primarily in the duodenum and proximal jejunum, is saturable, is energy dependent and involves a calcium binding protein. The $1,25(OH)_2D$-dependent absorption of calcium is stimulated by low dietary calcium intakes. The other route of intestinal calcium absorption is independent of $1,25(OH)_2D$ and is termed paracellular. This process is passive (does not depend on carrier proteins or energy) and occurs primarily in the jejunum and ileum. Calcium is absorbed between cells, rather than through cells, and down the concentration gradient. Calcium can be transported in blood bound to albumin and prealbumin; complexed with sulfate, phosphate, or citrate; or in a free (ionized) state.

Calcium is transported in blood bound to proteins (~40%), primarily albumin and prealbumin; complexed with sulfate, phosphate, or citrate (~10%); and in the ionized form (~50%). Blood calcium concentrations are controlled extracellularly by PTH, calcitriol, and calcitonin. Intracellular calcium concentrations are maintained at relatively low levels. Increased intracellular calcium concentrations occur in response to second messengers by stimulating release from intracellular sites (endoplasmic reticulum, mitochondria) and hormones by facilitating influx from extracellular sites by transmembrane diffusion or channels.

Calcium balance measures provide information on calcium absorption relative to calcium loss in urine, sweat, and endogenous intestinal secretions. During periods of growth, positive calcium balance implies bone mineralization but does not provide an indication of whether the rate of bone mineralization is optimal. During adulthood, negative calcium balance implies calcium lost from bone but does not provide an indication of which site(s). Calcium balances measures provide an indication of current but not prior calcium balance. An alternate approach to assessing bone mineralization is by measuring bone mineral density.

Approximately 99 percent of the calcium in the human body is in bone and teeth. In addition to structural roles, calcium has other critical functions. These include serving as a second messenger (e.g., cytosolic calcium, calcium-dependent trigger proteins, removal of calcium stimulus) and protein activator (e.g. phospholipase A_2, calpains [calcium dependent proteins that contain calmodulin-like domains], blood clotting enzymes, annexins [calcium and phospholipid binding proteins]). $1,25(OH)_2D$ plays a critical role in regulating plasma calcium concentrations through its role in intestinal calcium absorption, bone resorption, and renal calcium resorption. The functions of calcium are frequently classified into the following general categories: bone development and maintenance, blood clotting, transmission of nerve impulses to target cells, muscle contraction, and cell metabolism. In addition, calcium may play a role in colon cancer, kidney stones, blood pressure, body weight, and lead absorption.

Challenges for the DRI Committees

The following generic challenges must be addressed, preferably in a standardized way, before additional systematic reviews are conducted for use by upcoming DRI committees to ensure the resulting product will yield a maximally useful document.[5] Because the potential volume of peer reviewed literature on the biological effects of most essential nutrients is large

and continues to grow, rational and well defined eligibility criteria will need to be identified by the committee to manage the workload. Appropriate questions must be formulated so that the answers to those questions can be used to inform the DRI development process, ensure transparency and reproducibility, and serve as the foundation for future updates as new data emerge. Experience has shown that in the absence of unlimited resources, only a limited set of questions can be addressed. Hence, it is critical that the committee prioritize the topics and refine the questions in a way that will address critical issues for development and revision of DRI values.

Age specific intermediate or surrogate outcomes will need to be identified by the committee when few or no studies directly link specific nutrient intakes with clinical outcomes. Preferably, these would include only validated surrogates of the clinical outcome, that is outcomes that are strongly correlated with the clinical outcome (e.g., bone mineral density as a surrogate for fractures in postmenopausal women), and changes in their status reflect corresponding changes in the risk of the clinical outcome (e.g., changes in bone mineral density reflect changes in fracture risk in postmenopausal women).[22] In the absence of validated surrogate outcomes, intermediate outcomes must be identified and considered (e.g., absence of anemia as an intermediate outcome for the absence of disease or serum osteocalcin [bone turnover index] as an intermediate marker for fractures). When a nonvalidated intermediate outcome must be considered, the implicit assumption is that they would have the properties of a validated surrogate outcome. Not only should this assumption be made explicit, but the uncertainties involved in applying this assumption should be identified, documented, and discussed by the committee.

Reliable indicators of exposure (or biomarkers) need to be identified by the panel. A reliable biomarker should accurately reflect the degree of biological exposure to the nutrient of interest and fulfill the classic risk assessment model (e.g., exhibit a dose-response relationship). To that extent, the measurement of biological exposure should be independent and free from any interaction with the self-estimated intake of the nutrient of interest. It is important for the DRI committee to recognize that use of a biomarker to evaluate the strength of downstream associations requires that the biomarker concentrations be back translated into levels of nutrient intake and that if an association is found between a given biomarker concentration and risk of a clinical outcome, an estimate of the nutrient intake that corresponds to the clinical outcome will likewise be necessary.

Additional challenges for the DRI committees with respect to the conduct of systematic reviews include defining relevance of studied populations, with respect to nutrient distributions and health risks, to those for which reference values are being established, generalizability of well-controlled experiments with few subjects, generalizability of studies of subjects having narrow eligibility criteria, applicability for findings of animal studies to humans when data in humans are nonexistent, generalizability of early studies that used methodologies not considered state of the art or directly comparable with contemporary methods (e.g., change in analytical techniques or standardization), appropriate approaches to evaluating, interpreting and integrating data from observational studies with interventional data, and approaches to factor contemporary issues into the process, such as the role of genomics and nutrient fortification into the systematic review.

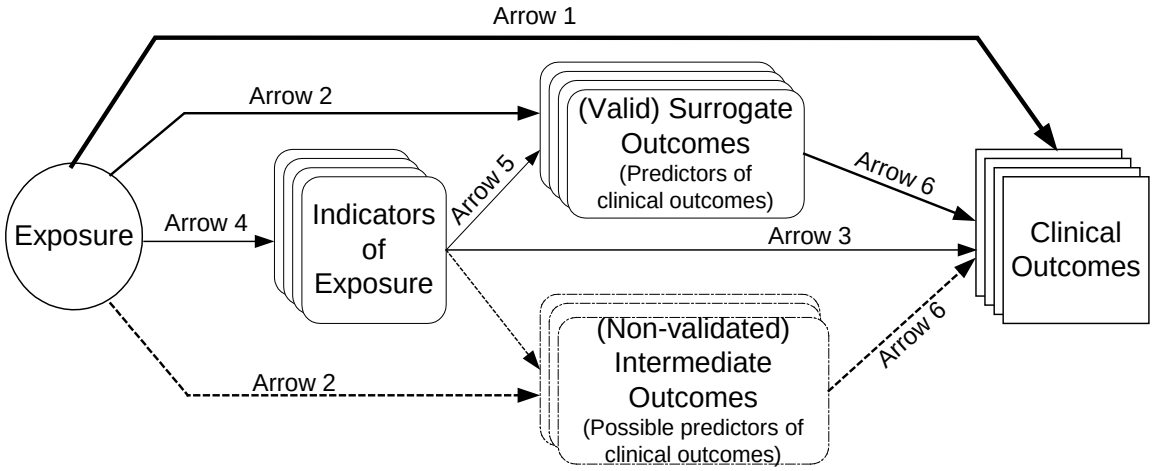
Key Questions Addressed in This Report

The aim of this report is to answer specific questions formulated to support the review and updating of DRI values by the DRI committee. The primary purpose of this report is to summarize all existing literature on vitamin D and calcium, and clinical outcomes in a way that will facilitate the deliberations of the IOM committee commissioned to review and potentially revise the DRI values for these nutrients. Specific clinical, surrogate and intermediate outcomes that are relating to vitamin D or calcium functions were selected by a technical expert panel. Detailed methods and analytic frameworks are described in the Methods chapter. The intent of this report is not to make recommendations on specific outcomes nor specific values for DRIs to be based upon; the intent of this report is to provide information for use during the deliberations of the IOM committee. The federal agencies of the U.S. and Canadian governments involved in the DRI process formulated the Key Questions listed below based on the generic analytic framework as recently described (Figure 2).[5] The Key Questions are:

- What is the effect of exposures on functional or clinical outcomes? (Arrow 1 in Figure 2)
- What is the effect of exposures on indicators of functional or clinical outcomes? (Arrow 2 in Figure 2)
- What is the effect of indicators of exposure or body stores on functional or clinical outcomes? (Arrow 3 in Figure 2)
- What is the effect of exposures on indicators of exposure? (Arrow 4 in Figure 2)
- What is the effect of indicators of exposure or body stores and intermediate indicators or outcomes? (Arrow 5 in Figure 2)
- What is the effect of intermediate indicators of outcomes on functional or clinical outcomes? (Arrow 6 in Figure 2)

For each of these questions, the mandate was to also address factors that affect these relationships.

Figure 2. Generic analytic framework to assist formulation of Key Questions for the development of DRIs



Arrow 1: Association of exposure with clinical outcomes of interest.
Arrow 2: Association of exposure with surrogate or intermediate outcomes (with good or possible evidence for linkage with clinical outcomes).
Arrow 3: Association of indicators of exposure to clinical outcomes.
Arrow 4: Association between exposure and indicators of exposure.
Arrow 5: Association of indicators of exposure to surrogate or intermediate outcomes (with good or possible evidence for linkage with clinical outcomes).
Arrow 6: Association between surrogate outcomes (with good or possible evidence for linkage) and clinical outcomes.

The focus of this evidence report is on the relationship of vitamin D only, calcium only **(not included in the update)**, and combinations of vitamin D and calcium to relevant health outcomes. Serum 25(OH)D concentration was used as an indicator of vitamin D status and calcium intake (dietary and supplement) as an indicator of calcium status. Evidence was sought for the life stages as defined in the DRI process. For the above questions, information relevant to benefit (efficacy) and safety (adverse effects) were considered. The questions were refined with input from a committee of vitamin D and calcium experts, as discussed in the Methods chapter.

Methods

Overview

This report is based on **two** systematic review**s** of Key Questions on the relationships between vitamin D [either 25(OH)D concentrations or supplements] or dietary calcium intake, and health outcomes. The methodologies employed in this evidence report generally follow the methods outlined in the AHRQ "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (http://effectivehealthcare.ahrq.gov/repFiles/2007_10Draft MethodsGuide.pdf). The initial questions identified by the federal sponsors of **the 2009** report were refined with input from a Technical Expert Panel (TEP). **The questions were modified slightly by the federal sponsor for the current report.** This report does not make clinical or policy recommendations. The original report was provided to an IOM committee charged with updating vitamin D and calcium DRIs.

A description of roles and responsibilities of **the original and current** sponsoring federal agencies, AHRQ, the TEP, and the EPCs is included to clarify the relationships that support the process and ensure transparency and that the approach adhered to the highest standards of scientific integrity.

Because of the large number of abbreviations for unfamiliar terms that are used, their explanations have been repeated whenever deemed necessary. A table of **Abbreviations** can be found after the references. We also provide a table with the latitudes of several major cities in Central and North America, right after the **Abbreviations** table.

Sponsoring Federal Agencies

The sponsoring agencies **(a single agency for the current report)** were responsible for specifying the topic-specific task order requirements. They participated in a kickoff meeting with the EPC and the Task Order Officer (TOO) to facilitate a common understanding of the topic-specific work requirements, and responded to inquiries from the TOO if modifications to the work order were requested by the EPC. Any communication between the sponsoring agencies and the EPC occurred with oversight from the TOO.

Review by the Federal sponsor was limited to comments on factual errors, requests for clarification, and monitoring for consistency with the original contract task order. Comments on the scientific content of the report were not provided. In all cases, reviewer comments are advisory only and are not binding on the scientific authors of the final report.

AHRQ Task Order Officer

The TOO was responsible for overseeing all aspects of this Task Order. The TOO served as the point person for all communication required between the sponsoring agencies, the EPC, and other AHRQ officials. The purpose of this communication was to facilitate a common understanding of the task order requirements among the sponsors, the TOO, and the EPC; resolve ambiguities; and allow the EPC to focus on the scientific issues and activities.

Technical Expert Panel

The Technical Expert Panel (TEP) comprises qualified experts including, but not limited to, individuals with knowledge of DRI decisionmaking processes, vitamin D and calcium nutrition

and biology across the life cycle, health outcomes of interest, and the methodology of conducting systematic reviews. The EPC worked closely with the TEP in the formative stages of the project on question refinement and throughout the evidence review process to address questions that occurred. The EPC conducted the actual systematic review of the questions independent of the TEP and other stakeholders. It was specified, a priori, that a TEP member who served as a peer reviewer for the final report could not also serve as a member of the subsequent calcium and vitamin D DRI Committee.

Those serving on the TEP provided input on such factors as reviewing search terms to ensure they were adequately inclusive, assessing search strategies to ensure they comprehensively covered the questions of interest, and answering questions about technical details (e.g., nuances of laboratory methods of performing an assay). Members of the TEP did not participate in EPC research meetings or in reviewing and synthesizing evidence. Their function was limited to providing domain-specific knowledge and advising the proper context that is relevant to the process of evaluating DRIs. They did not have any decisionmaking role and did not participate in writing any part of the evidence report.

EPC Methodologists

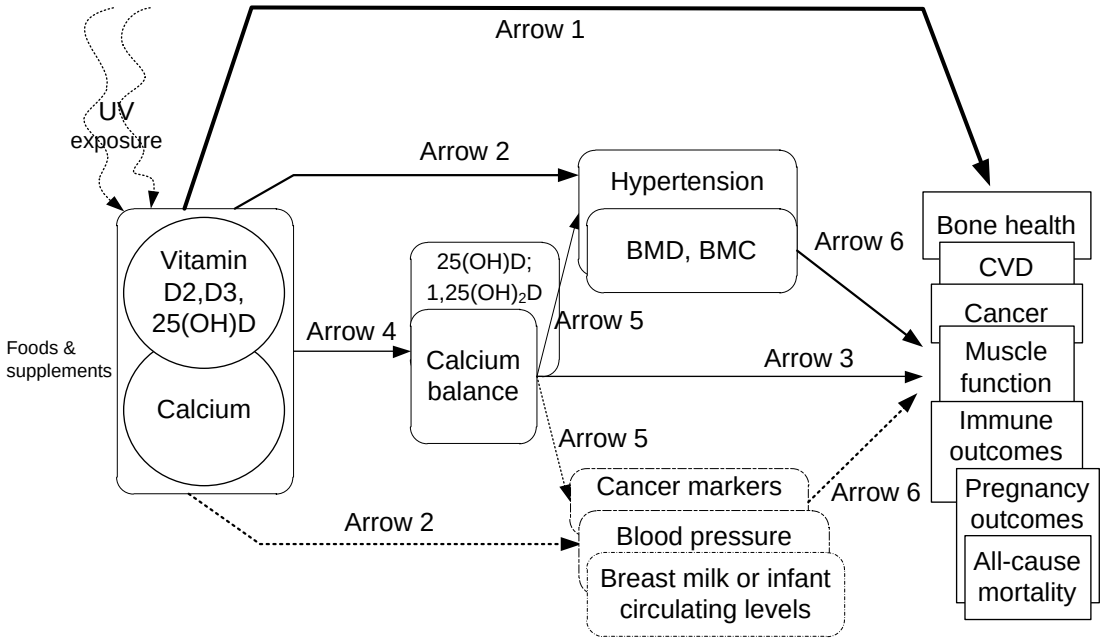
This evidence report was carried out under the AHRQ EPC program, which has a 16-year history of producing hundreds of evidence reports and numerous technology assessments for various users including many federal agencies. EPCs are staffed by experienced methodologists who continually refine approaches to conducting evidence reviews and develop new methods on the basis of accumulated experience encompassing a wide range of topics. The Tufts EPC **and RAND EPC** have produced many evidence reports on nutrition topics.[23-32] (www.ahrq.gov/research/findings/evidence-based-reports/index.html). We have also conducted methodological research to identify the issues and challenges of including evidence-based methods as a component of the process used to develop nutrient reference values, such as the DRIs, using vitamin A as an example.[5]

Development of the Analytic Framework and Refinement of Key Questions

The focus of this report is on the relationship of vitamin D only, calcium only **(excluded in the update report)**, and combinations of vitamin D and calcium with specific health outcomes. Key questions and analytic frameworks were developed by defining each box in the generic analytic framework described in the Introduction with specific reference to vitamin D and calcium.

A one-day meeting of the federal sponsors, TEP, and Tufts EPC staff was held in Boston on September 20, 2008. At this meeting, the analytic framework was discussed, the Key Questions refined, and study eligibility criteria established. Two analytic frameworks were developed: one for vitamin D and/or calcium Estimated Average Requirements (EARs) and one for Tolerable Upper Intake Levels (ULs) (Figures 3 & 4). We used the PI(E)CO method to establish study eligibility criteria. This method defines the Population, Interventions (or Exposure in the case of observational studies), Comparators, and Outcomes of interest. Details are described in the sections that follow.

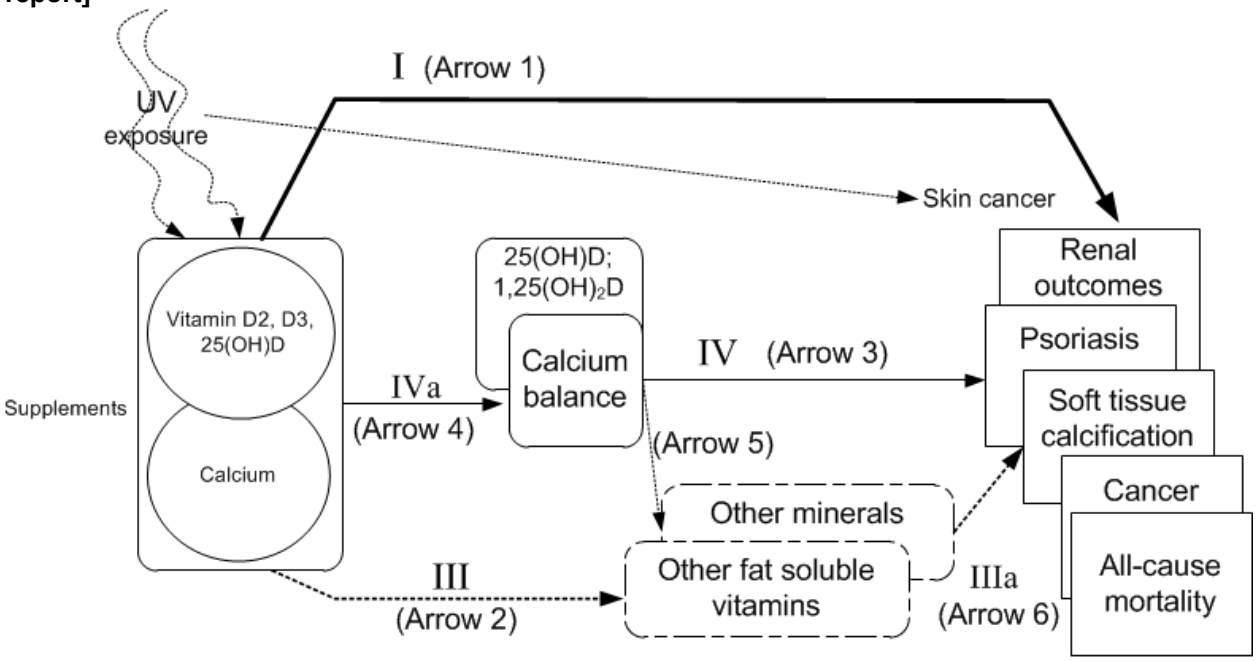
Figure 3. Analytic framework for vitamin D with or without calcium: EARs [revised for the current report]



EARs
Arrow 1: Association of exposure with clinical outcomes of interest.
Arrow 2: Association of exposure with surrogate or intermediate outcomes (that have, respectively, good or possible evidence for linkage with clinical outcomes). (Surrogate outcomes are depicted in boxes with a solid outline, and intermediate outcomes are depicted in boxes with dashed outline.)
Arrow 3: Association of indicators of exposure to clinical outcomes.
Arrow 4: Association between exposure and indicators of exposure.
Arrow 5: Association of indicators of exposure to surrogate or intermediate outcomes.
Arrow 6: Association between surrogate or intermediate outcomes and clinical outcomes.

Abbreviations: $1,25(OH)_2D$ = 1,25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D;BMC = bone mineral content; BMD = bone mineral density; CVD = cardiovascular disease; UV = ultraviolet light

Figure 4. Analytic framework for vitamin D with or without calcium ULs [revised for the current report]



Arrow 1: Association of exposure with clinical outcomes of interest.
Arrow 2: Association of exposure with surrogate or intermediate outcomes (that have, respectively, good or possible evidence for linkage with clinical outcomes). (Surrogate outcomes are depicted in boxes with a solid outline, and intermediate outcomes are depicted in boxes with dashed outline.)
Arrow 3: Association of indicators of exposure to clinical outcomes.
Arrow 4: Association between exposure and indicators of exposure.

Abbreviations: 1,25(OH)2D = 1,25-dihydroxyvitamin D; 25(OH)D = 25-hydroxyvitamin D; UV = ultraviolet light

Definitions

Vitamin D and Calcium Exposures

Vitamin D exposure included intake of vitamin D_2 or vitamin D_3 from foods and supplements, including human milk and commercial infant formulas. Because the primary source of vitamin D in the human body is from skin exposed to sunlight, background information on ultraviolet B (UVB) exposure was captured to the extent possible. However, we did not include studies that evaluated the effect of or association between exposure to sunlight (or UVB) and clinical outcomes or serum 25(OH)D concentrations. In other words, we did not investigate sunlight exposure as a proxy for or a source of vitamin D intake. Sunlight exposure was considered only as a potential confounder or effect modifier of associations between vitamin D or calcium and clinical outcomes.

Calcium exposure included intake of calcium from foods and supplements, including calcium-containing antacids, mineral-supplemented water, human milk and commercial infant formulas.

Combined vitamin D and calcium exposure included any relevant combinations of the above.

Clinical Outcomes

Clinical outcomes are measures of how a person (e.g., a study participant) feels, functions, or survives, or a clinical measurement of the incidence or severity of a disease (e.g., diagnosis of disease or change from one disease state to another). Examples of clinical outcomes used in this report are incidence of cancer, vascular events, and preeclampsia. The clinical outcomes of interest in this report are described in the "Specific Outcomes of Interest" section.

Indicators of Exposure (Nutrient Intake)

Indicators of exposure are measures that correlate with dietary intake of a nutrient, such as nutrient biomarkers, nutritional status, or markers of nutritional status.

Indicators of vitamin D exposure (i.e., vitamin D intake and sun exposure) included serum 25(OH)D and 1,25$(OH)_2$D concentrations.

Indicators of dietary calcium intakes included calcium balance (i.e., calcium accretion, retention, and loss).

Surrogate Outcomes

Surrogate outcomes are biomarkers or physical measures that are generally accepted as substitutes for or predictors of specific clinical outcomes.[22] Changes induced by the exposure or intervention on a surrogate outcome marker are expected to reflect changes in a clinical outcome. Examples of surrogate outcomes used in this report are bone mineral density (as a surrogate marker of fracture risk) and breast mammographic density (as a surrogate marker of breast cancer risk). The surrogate outcomes of interest in this report are described in "Specific Outcomes of Interest" section.

Intermediate Outcomes

Intermediate outcomes are possible predictors of clinical outcomes that are not generally accepted as fulfilling the criteria for a surrogate outcome. However, in the absence of data for surrogate outcomes, intermediate markers are often used. Examples of intermediate markers used in this report are prostate cancer antigen (as a marker of prostate cancer risk) and blood pressure (as a marker of stroke risk). All intermediate markers of interest in this report are described in the "Specific Outcomes of Interest" section.

Life Stages

In consultation with the TEP, the 22 life stages defined by the FNB/IOM for the development of DRIs were consolidated to 9 categories to facilitate the reporting of results. Within each life stages, men and women (or boys and girls) were considered separately when possible. There are also some inevitable overlaps between these categories. For example, most women in the 51–70 years life stage are postmenopausal women. The 9 categories created for this report are:

- 0–6 months
- 7 months–2 years
- 3–8 years
- 9–18 years
- 19–50 years
- 51–70 years

- ≥71 years
- Pregnant and lactating women
- Postmenopausal women

In summarizing studies for each given outcome, we used our best judgment to describe the study results for each applicable life stage.

Key Questions

In agreement with the TEP, the following Key Questions were addressed in this evidence report. It was decided that arrow 6 in the analytic framework (What is the relationships between intermediate or surrogate outcomes and clinical outcomes?) is outside the scope of the DRI literature review in this report. All outcomes of interest in this report are described in the "Eligibility Criteria" section. **The questions shown reflect the revisions for the update report.**

Key Question 1. What is the effect of vitamin D, calcium **(excluded from update report)**, or combined vitamin D and calcium intakes on clinical outcomes, including growth, cardiovascular diseases, weight outcomes, cancer, immune function, pregnancy or birth outcomes, mortality, fracture, renal outcomes, and soft tissue calcification **(the update report excludes the outcomes of postnatal growth and weight outcomes)**? (Arrow 1 in Figure 2)

Key Question 2. What is the effect of vitamin D, calcium**(excluded from update report),** or combined vitamin D and calcium intakes on surrogate or intermediate outcomes, such as hypertension, blood pressure, and bone mineral density? (Arrow 2 in Figure 2)

Key Question 3. What is the association between serum 25(OH)D concentrations or calcium balance **(excluded from update report)** and clinical outcomes? (Arrow 3 in Figure 2)

Key Question 4. What is the effect of vitamin D or combined vitamin D and calcium intakes on serum 25(OH)D concentrations? (Arrow 4 in Figure 2)

Key Question 5. What is the association between serum 25(OH)D concentrations and surrogate or intermediate outcomes? (Arrow 5 in Figure 2)

Literature Search Strategy

We conducted a comprehensive literature search to address the Key Questions. For primary studies, the EPC used the Ovid search engine to conduct searches in the MEDLINE® and Cochrane Central database. A wide variety of search terms were used to capture the many potential sources of information related to the various outcomes (see Appendix A). Search terms that were used to identify outcomes of interest, for both EARs and ULs, can be categorized into the following groups: (1) body weight or body mass index; (2) growth (height and weight); (3) fracture or bone mineral density; (4) falls or muscle strength; (5) cardiovascular diseases; (6) hypertension or blood pressure; (7) cancer or neoplasms, including adenomas, colon polyps, and mammography; (8) autoimmune diseases (e.g., type 1 diabetes, psoriasis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, and Crohn's disease); (9) preeclampsia, eclampsia, and pregnancy-related hypertension; (10) preterm or low birth weight; (11) breast milk or lactation; (12) death; (13) infectious diseases; (14) soft tissue calcification (for ULs only); and (15) kidney disease or hypercalcemia (for ULs only). The different outcomes were crossed with terms to identify vitamin D and calcium exposure: "vitamin D," "plasma vitamin D," "25-hydroxyvitamin D" and its abbreviations, "25-hydroxycholecalciferol," "25-hydroxyergocalciferol," "calcidiol," "calcifediol," "ergocalciferol," "cholecalciferol," "calciferol," "calcium," "calcium carbonate," "calcium citrate," "calcium phosphates," and "calcium malate." Literature searches of the outcomes alone without references to vitamin D or calcium were not conducted.

The searches were limited to human studies, English language publications, and citations from 1969 to September 2008 for all but bone outcomes. For outcomes related to bone health (i.e., bone mineral density, fracture, fall or muscle strength), we relied on a recent comprehensive systematic review performed by the Ottawa EPC.[8] The Ottawa EPC report was updated from January 2006 to September 2008. The electronic search was supplemented by bibliographies of relevant review articles. Unpublished data, including abstracts and conference proceedings, were not included. An updated literature search was performed in April 2009 for all the topics to include relevant primary studies published since September 2008 for the final report.

For potentially relevant systematic reviews, we also searched MEDLINE®, the Cochrane Database of Systemic Reviews, and the Health Technology Assessments database up to December 2008. We searched for systematic reviews of the relationships between vitamin D or calcium and the prespecified outcomes. In this search, terms for identifying vitamin D or calcium exposures were crossed with terms for identifying systematic reviews, such as "systematic," "evidence," "evidence-based," "meta-analysis," or "pooled analysis"; specific terms for the outcomes were not included (Appendix B).

The search strategy of peer-reviewed literature for the update report duplicated that used in the original 2009 report to the extent possible, excluding the searches specific to calcium only and those for the outcomes of growth and weight. The librarian at the RAND Southern California Evidence-based Practice Center reviewed and modified the search strategies as needed and ran the searches in Medline® and the Cochrane Central Database from January 2008 to December 30, 2013 (see Appendix A).

In addition, at the request of AHRQ, in lieu of contacting each U.S. manufacturer of vitamin D supplements for product information and results of any unpublished studies, a notice was placed in the *Federal Register* on Thursday, July 18, 2013, requesting scientific information submissions (https://www.federalregister.gov/articles/2013/07/18/2013-

17177/scientific-information-request-on-vitamin-d-and-calcium**). One draft journal article submission was received.**

Study Selection

Abstract Screening

All abstracts identified through the literature search were screened. Eligible studies included all English language primary interventional or observational studies that reported any outcome of interest in human subjects in relation to vitamin D and/or calcium **[for the update, we sought only studies of vitamin D or vitamin D and calcium]**.

Full-Text Article Eligibility Criteria

Articles that potentially met eligibility criteria at the abstract screening stage were retrieved and the full text articles were reviewed for eligibility. Rejected full text articles were examined only once, unless the articles were equivocal for inclusion or exclusion. In that event, the article in question was examined again by a different reviewer and a consensus was reached after discussion with the first reviewer. We recorded the reason for rejection of all full text articles.

Primary Studies

Because the outcomes of interest ranged from very broad topics with common occurrences (e.g., cardiovascular disease) to narrowly focused topics with relatively few occurrences (e.g., preeclampsia), the number and types of studies available for each outcome varied widely in the distribution of study designs and sample sizes. It was neither possible nor desirable to use a uniform, strict set of inclusion and exclusion criteria applicable to all outcomes. Therefore, additional eligibility criteria germane to the specific outcome were applied to all accepted full text articles. Details are described in the “Eligibility criteria” section.

General eligibility criteria for the full text articles were:

Population of Interest

- Primary population of interest is generally healthy people with no known disorders

Studies that include a broad population that might have included some people with diseases. For example, some hypertensive and diabetic patients were included.

- People with prior cancers (or cancer survivors), prior fractures, and precancer conditions (e.g., colon polyps) were included.
- Studies that enrolled more than 20% subjects with any diseases at baseline were excluded. An exception was made for older adults (mean age ≥65 years old) due to high prevalence of diseases in this population. For studies of older adults, only studies that exclusively enrolled subjects with particular disease (e.g., 100% with type 2 diabetes) were excluded. In addition, for studies of blood pressure, studies of people exclusively with hypertension were included.
- For UL outcomes, we included any adverse effects of high intake in any population.

Intervention/Exposure of Interest

- For observational studies:

    - Serum 25(OH)D or 1,25$(OH)_2$D concentration
    - Dietary intake level of vitamin D were not included due to inadequacy of nutrient composition tables for vitamin D.[33]
    - Dietary intake level of calcium from food and/or supplements **[excluded for update]**
    - Calcium balance (i.e., calcium accretion, retention, and loss) **[excluded for update]**
- For interventional studies:
    - Vitamin D supplements (but not analogues) with known doses
    - Calcium supplements with known doses **[for update, only if accompanied by vitamin D or administered as part of placebo]**
    - The only combination of dietary supplements of interest was the combination of vitamin D and calcium. Any other combinations of supplements and/or drug treatments were excluded unless the independent effects of vitamin D and/or calcium could be separated. Thus studies of multivitamins were excluded.
    - Trials in which participants in both study groups took the same calcium (or vitamin D) supplement were evaluated as vitamin D (or calcium) versus control trials. In other words, the intervention common to both study groups was ignored (though it was noted).
    - Food based interventions were included if the doses of vitamin D and/or calcium were quantified and there were differences in the doses between the comparison groups. For example, a trial of dairy supplementation (with 500 mg/d calcium) versus no supplementation was qualified to be included. However, a trial of calcium fortified orange juice (with 1200 mg/d calcium) versus milk (with 1200 mg/d calcium) was not qualified to be included because there are no differences in the calcium doses.
    - Non-oral routes of nutrient delivery were excluded

Specific Outcomes of Interest

- Growth outcomes **[excluded from update]**
    - In infants and premenarchal children: weight and height gain
- Cardiovascular disease clinical outcomes
    - Cardiac events or symptoms (e.g., myocardial infarction, angina)
    - Cerebrovascular events (stroke, transient ischemic attacks)
    - Peripheral vascular events or symptoms (diagnosis, claudication)
    - Cardiovascular death
    - Study-specific combinations of cardiovascular events
- CVD intermediate outcomes
    - Diagnosis of hypertension
    - Blood pressure
- Weight outcomes **[excluded from update]**
    - In adults only: incident overweight or obesity, body mass index, or weight (kg)
- Cancer (incident or mortality)
    - Cancer from all cause (or total cancer)
    - Prostate
    - Colorectal cancer

    - Breast cancer
    - Pancreatic cancer
    - Cancer-specific mortality
- Cancer intermediate outcomes
    - Colorectal adenoma
    - Aberrant cryptic
    - Breast mammographic density (quantitative whole breast density)
- Immune function clinical outcomes
    - Infectious diseases
    - Autoimmune diseases
    - Infectious disease-specific mortality
- Pregnancy-related outcomes
    - Preeclampsia
    - High blood pressure with or without proteinuria
    - Preterm birth or low birth weight
    - Infant mortality
- Mortality, all cause
- Bone health clinical outcomes
    - Rickets
    - Fracture
    - Falls or muscle strength
- Bone health intermediate outcomes
    - Bone mineral density or bone mineral content
- Dose-response relationship between intake levels and indicators of exposure (arrow 4 in Figures 2 and 3)
    - Serum 25(OH)D concentration
    - Breast milk or circulating concentrations of 25(OH)D in infants
- Outcomes of tolerable upper intake levels (ULs)
    - All-cause mortality
    - Cancer and cancer-specific mortality
    - Renal outcomes
    - Soft tissue calcification
    - Adverse events from vitamin D and/or calcium supplements

Study Design

- Randomized controlled trials (RCTs)
- Nonrandomized, prospective comparative studies of interventions
- Prospective, longitudinal, observational studies (where the measure of exposure occurred before the outcome)
- Prospective nested case-control studies (case-control study nested in a cohort so the measure of exposure occurred before the outcome)
- We excluded cross-sectional studies and traditional, retrospective case-control studies (where the measure of exposure occurred after or concurrent with the outcome)

Systematic Reviews

We included relevant systematic reviews that addressed the Key Questions. Systematic review is defined as a study that has at a minimum the following three components: a statement of the research questions (aims or objectives); a description of the literature search; and a listing of the study eligibility criteria. We did not attempt to contact authors for clarifications of outstanding questions. In addition, the following types of reviews were excluded: reviews of foods or diets that did not quantify vitamin D or calcium intake; reviews that included non-oral routes of nutrient delivery; reviews that did not evaluate the association between vitamin D or calcium intake and health outcomes; reviews of nonhuman data; and pooled analyses of primary databases (i.e., secondary database analyses of multiple cohorts) that did not include a systematic review (except possibly as a replacement for data from the original cohorts).

To determine the relevance of a systematic review to this report, the following inclusion criteria were applied:

- Address Key Question(s) of interest (i.e., similar PI(E)CO criteria used):
    a. Systematic review must include only healthy population at baseline or have separate analyses for population with diseases and without diseases.
    b. Systematic reviews of interventional studies had to include only vitamin D or calcium interventions. Cointerventions with other nutrients had to be disallowed or separate analyses were needed for studies of vitamin D or calcium interventions alone.
    c. Systematic review of observational studies had to report the baseline concentrations of serum 25(OH)D and the assay methods used or the dietary assessment methods used to measure dietary calcium intake (e.g. food frequency questionnaire, 24 hour recall).
    d. Exposure levels (e.g., level of 25(OH)D or calcium intake) or doses of interventions had to be reported
    e. Outcome definitions had to be reported
    f. Designs of primary studies had to be reported. If cross-sectional or case-control studies were included, the systematic review must provide sufficient information or separate analyses to separate them from RCTs or cohort studies.
- We include only the most recent update if there were multiple systematic reviews from the same group of investigators using the same review process.
- Where there were several systematic reviews on the same topic with similar conclusions and the same set of primary studies, we selected the systematic review with either the latest cutoff date for the end of the literature search or the most included primary studies. Where there were several systematic reviews, each of which included only a sample of the total literature included by the several systematic reviews, all systematic reviews were included.

Other Specific Eligibility Criteria

- Growth outcomes (weight and height gain) **[excluded from update]**
    - Only infants (<1 year old) and children (age <18 years old) were included
    - For infants, we include all eligible study designs. The vitamin D and/or calcium intervention or exposure can be administered to the mothers or to the infants in the study.

    - For infants, premenarchal girls, and boys of similar age, only RCTs that reported weight as a primary or secondary outcome were included. RCTs of weight loss were excluded.
- Cardiovascular disease clinical outcomes
    - Only adults (aged ≥18 years old) were included.
- Blood pressure and body weight
    - Only adults (aged ≥18 years old) were included.
    - Only RCTs of calcium or vitamin D **[only vitamin D or vitamin D and calcium for update]** interventions were included. We did not include observational studies of associations between calcium or vitamin D intake or serum vitamin D concentrations and blood pressure or weight measurements (as continuous outcomes). This decision was made in agreement with the TEP in part because it was agreed that any conclusions based on observational studies (e.g., associations between baseline calcium intake and change in systolic blood pressure) would be weak and difficult to interpret.
- Bone health clinical outcomes
    - The Ottawa EPC report[8] was updated with literature published between January 2006 and September 2008. Only RCTs qualified for inclusion.
    - Studies of calcium and bone health clinical outcomes were excluded.
- Bone health intermediate outcomes
    - The Ottawa EPC report[8] was updated with literature published between January 2006 and September 2008. For adults, we included only BMD indices. For children, we included only BMC indices. Only RCTs with duration of more than 1 year were qualified for inclusion.
    - Studies of calcium and bone health clinical outcomes were excluded.
- Dose-response relationship between intake levels and indicators of exposure (arrow 4 of Figures 2 and 3)
    - Studies for this question were identified in our literature search that crossed vitamin D terms with various outcomes terms. Some studies that addressed this question but did not report any of the outcomes of interest would not have been identified in this manner. Because the availability of serum 25(OH)D concentration is unlikely to be adequately indexed in the MEDLINE® citation, it would be difficult to comprehensively search the literature for this question. To do so would require retrieving all full text articles mentioning vitamin D supplements (in excess of 10,000) to look for data on serum 25(OH)D concentration.
    - Only RCTs were included for this question. However, RCTs of different regimens but with the same dose of vitamin D supplementation were excluded (e.g., comparison of daily, weekly versus monthly dose).

Data Extraction

For outcomes that had not been subjected to a prior systematic review, we extracted and summarized the relevant data from the primary studies. Where previous systematic reviews were available, we summarized their results into our report. In addition, we updated the previous systematic reviews (with our eligibility criteria) and extracted and summarized the additional primary studies. **For the update, we extracted data from all original studies that satisfied the**

inclusions/exclusion criteria and were published since the original 2009 report. For a small number of outcomes, we identified and report the conclusions of systematic reviews that we determined to be of high quality.

Data extraction forms (evidence tables) were developed separately for extraction of systematic reviews and primary studies. For primary studies, the items extracted were: study characteristics, baseline population characteristics, background diet data, dietary assessment methods for calcium intake, 25(OH)D assay methods **(including location and date of assay performance; manufacturer of kit, if used; coefficients of variation; and reference standard, if described [the reference standard refers to a sample whose concentration of 25(OH)D has been ascertained by a recognized entity, such as the United States National Institute of Standards and Technology (NIST), that is used to establish the reliability of an assay])**, interventions (for interventional studies only), confounders and effect modifiers that were adjusted for in statistical analysis, results, and quality assessments. Whenever the type of vitamin D supplement (D_2 or D_3) was clearly reported, we extracted and reported this information. Otherwise, we used the general term "vitamin D". **For the update, DistillerSR™ was used for data extraction.** Evidence tables for all eligible studies are available in Appendix C. For systematic reviews, items extracted were: design, population, intervention (exposure) and comparator, results, and AMSTAR[34] checklist criteria (a measurement tool created to assess the methodological quality of systematic reviews). A table with a list of all systematic reviews with the evaluation of their relevance to this report, and evidence tables of the qualified systematic reviews are available in Appendix D.

All data abstracted for the report will reside on the Systematic Review Data Repository; data for the 2009 report currently reside at this site.

Data Analysis

We explored the dose-response relationship between the level of intake of vitamin D (with or without calcium) and serum 25(OH)D concentrations graphically, using a scatter ("bubble") plot. We plotted the observed net changes in 25(OH)D concentration, against the doses of vitamin D supplementation. In these plots studies were represented by empty circles (bubbles) with area proportional to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D. **For the update, we reported the data for dose-response outcomes by assay method, to the extent the assay method could be identified from the study report. A table of assay methods, locations, dates, precision, and standards for each controlled trial included in the original and update reports appears in Appendix G. Key outcomes stratified by assay method are shown in Appendix H.**

Studies were included only if they reported sufficient data to estimate both mean net change and SE of the net change. We required data on both the mean net change in outcome level and the SE of the change. However, many studies provided only the SEs for the baseline and final outcome levels. In order to include these studies in the analyses we had to make several assumptions to estimate the SE of the change. To do this we used the equation:

$$SE_{12} = \sqrt{(SE_1^2 + SE_2^2 - 2\rho SE_1 SE_2)}$$

where SE_1, SE_2, and SE_{12} are the SEs for baseline, final and change, respectively, and ρ is the correlation between the baseline and final measurements.[35] We arbitrarily chose the correlation, ρ, to be 0.50, the midpoint value. In our experience, using different values for ρ generally does not greatly affect the meta-analysis results of quantitative analyses or conclusions.

For each RCT, the SE of the net change was then calculated using the standard calculation for determining the SE of 2 independent cohorts. Namely, in the above equation where the correlation factor ρ becomes 0, and thus the final term drops out. Where studies reported either within-cohort SEs or net change SEs, these numbers were used. Some RCTs may have more than two arms (e.g., two different doses of vitamin D supplement compared to the placebo), and in this case, the same control arm was used to calculate the net change and the SE of the net change as for two independent comparisons.

Meta-Analysis

Overall, we did not perform new meta-analyses in this report because of the large degree of clinical and methodological heterogeneity across studies. However, **the original report** reanalyzed an existing meta-analysis using available data in the all-cause mortality section. **That report** performed random effects model meta-analyses of risk ratios using the DerSimonian and Laird model.[36] The random effects model assigns a weight to each study that is based both on the individual study variance and the between-study heterogeneity. Compared with the fixed effect model, the random effects model is more conservative in that it results in broader confidence intervals when between-study heterogeneity is present. Heterogeneity was tested using Cochran's Q (considered significant for $P < 0.10$) and quantified its extent with I^2.[37,38] I^2 ranges between 0 and 100 percent and quantifies the proportion of between-study variability that is attributed to heterogeneity rather than chance.

Intercooled Stata SE version 9.2 and Meta-Analyst version 3.2 (developed by Tufts EPC) were used for analyses. All P values are two tailed and considered significant when less than 0.05, unless otherwise indicated.

Grading of Studies Analyzed in This Evidence Report

Studies included in this report have been designed, conducted, analyzed, and reported with various degrees of methodological rigor and completeness. Deficiencies in any of these items may lead to biased reporting or interpretation of the results. Although the quality of evidence is multidimensional and a single metric cannot adequately capture information needed to interpret a study, it is desirable to have a simple evidence grading system using a single quantity. The grading system employed for AHRQ EPC reports was adapted as described below.

Critical Appraisal and Grading of Primary Studies

Critical appraisal of the evidence is an important aspect of conducting a systematic review. For the assessment of interventional studies, the criteria were based on the CONSORT[39] statement for reporting RCTs (a checklist with specifications for reporting important aspects of a trial). We primarily considered the methods used for randomization, allocation concealment, and blinding as well as the use of intention-to-treat analysis, the report of well-described valid primary outcomes, and the dropout rate.

For interventional studies with nonrandomized design, we used the report of eligibility criteria and assessed the adequacy of controlling for differences between compared groups in terms of baseline characteristics and prognostic factors. We also considered the reporting of intention-to-treat analyses and crossovers when so designed, as well as important differential loss to follow up between the compared groups or overall high loss to follow up. The validity and the adequate description of outcomes and results were also assessed.

For the assessment of prospective cohorts and nested case-control studies (cross-sectional and retrospective case-control studies were excluded from this review), we developed a rating checklist specifically designed for nutritional epidemiology studies based on some of the reporting items for cohort study in STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) checklist[40] and the nutrition-specific items in our previous publication.[41] Items assessed include: eligibility criteria and sampling of study population, blinding of exposure and outcome assessors, dietary assessment methodology (when applicable), assay methodology of biomarkers of intake (when applicable), clear reporting of comparisons in the study, statistical analyses, adequacy of controlling for baseline characteristics and prognostic factors (including confounders), clear reporting of outcome definitions, and prospective study design with preplanned hypotheses.

The quality assessment checklists for intervention or observational studies can be found in Appendix E. Additional considerations that were not included in the checklists are described later in this section.

In this report we adapted a three-category grading system of the AHRQ Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. This system defines a generic grading system that is applicable to each type of study design including interventional and observational studies:

Grade A

Studies have the least bias and results are considered valid. These studies adhere mostly to the commonly held concepts of high quality including the following: a formal study design; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; clear reporting of dropouts; and no obvious bias. Studies must provide valid estimation of nutrient exposure, from dietary assessments and/or biomarkers with reasonable ranges of measurement errors, and justifications for approaches to control for confounding in their design and analyses.

Grade B

Studies are susceptible to some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category “A,” they have some deficiencies but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

Grade C

Studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; there are large amounts of missing information or discrepancies in reporting.

If the initial assigned grade was equivocal, then the study received a second round of review by an independent reviewer, and the final grade was reached via consensus. Lastly, it should be noted that the quality grading system evaluates and grades the studies within their own design strata (i.e., RCTs, cohorts, nested case-control). It does not attempt to assess the comparative validity of studies across different design strata. Thus, it is important to be cognizant of the study design when interpreting the methodological quality grade of a study.

Additional Considerations of Methodological Quality of Primary Studies for the Purpose of DRI Decisionmaking

Randomized Controlled Trials of All Outcomes

The Tufts EPC debated about the quality assessment of RCTs. A consensus was reached to include additional considerations for RCTs to receive grade A. The general quality assessment of interventional studies as described earlier has been widely adopted for the purpose of grading high quality effectiveness trials (in contrast with a more standardized efficacy trial) which are most relevant to the actual use of supplements. Thus the crossover of interventions (i.e., contamination between supplementation and placebo groups) affects the applicability more than the methodological quality. However, it was the consensus among the Tufts EPC methodologists that the RCTs with contamination between supplementation and placebo groups cannot receive grade A because this issue affects the actual differences in the doses given to the subjects. Therefore it is particularly important when the trial results are used to guide decisions about DRIs, as opposed to decisions about whether to actively recommend supplementation for an individual.

Observational Studies of Cancer Outcomes

When cancer cases were identified based on cancer registries or questionnaire-based data, we perused whether the investigators verified the diagnoses independently (e.g., by medical records or pathological reports). An observational study of cancer outcomes could not receive grade A if the cancer diagnoses were not verified independently. We also examined if the study adequately controlled for other risk factors for the specific cancer. We used the suggested risk factors by American Cancer Society (www.cancer.org). An observational study of cancer outcomes could not receive grade A if important risk factors for the specific cancer were not fully controlled for in their analyses.

Critical Appraisal of Systematic Reviews

We also critically appraised systematic reviews utilized in this report. However, a summary quality grade for systematic review is difficult to interpret. While it may be straightforward to assign a high quality grade to a rigorously carried out systematic review of high quality primary studies, a rigorously conducted systematic review finding only poor quality primary studies to summarize has uncertain value. Similarly, a poorly conducted systematic review of high quality studies may also result in be misleading conclusions. Therefore, to appreciate its validity, the various dimensions and nuances of the systematic review must be understood.

To help readers appreciate the methodological quality of a systematic review, we applied the AMSTAR checklist,[34] a tool that was created for this purpose. This tool does not assign a composite grade. Instead, the items evaluated are made explicit for the reader. Another challenge in evaluating systematic reviews is that none of the existing systematic reviews were specifically conducted to be used for DRI development; therefore their “quality”, for the purpose of DRI development, is impossible to reliably define.

In addition to using AMSTAR, we made comments on special considerations, issues or limitations concerning design, conduct and analyses of the systematic review, and interpretability of the results for the purpose of DRI development.

Reporting of the Evidence

Evidence Tables

Evidence tables offer a detailed description of the primary studies we identified that address each of the Key Questions. These tables provide detailed information about the study design, patient characteristics, background diet, inclusion and exclusion criteria, interventions (or exposures), comparators used, and outcomes assessed in the study. A study, regardless of how many interventions (or exposures) or outcomes were reported, appears once in the evidence tables. Evidence tables are ordered alphabetically by the first author's last name to allow for easy searching within the tables. Evidence tables are available electronically in Appendix C.

Summary Tables

Summary tables were created to assist (qualitative) synthesis of primary studies of the same outcomes and life stage. If feasible, data were also grouped by sex. Typically, in each outcome section, we presented one summary table for the study characteristics of all included studies, followed by another summary table for study findings.

We created different summary tables for different exposures (i.e., vitamin D or calcium) and for different study designs (i.e., interventional or observational studies). Key study characteristics, such as population characteristics (i.e., health status, age and sex), vitamin D assay method and season in which blood was drawn, dietary assessment methods and whether the instrument was internally validated, patient or participant adherence, and study comparisons, were presented in the summary table for study characteristics. We reported daily vitamin D doses (IU/d) and/or elemental calcium doses (mg/d) in all summary tables.

For observational studies, we also list the confounders adjusted for in either design (e.g., matching factors) or analyses. If any confounders or effect modifiers in each prespecified category (i.e., nutrients, demographics, anthropometry, medical conditions, ultraviolet exposure, and lifestyles) were controlled for, we marked "X" in that category. Otherwise, the category was left blank. **The full list of potential confounders for which new studies for this update controlled are listed with those studies in the evidence tables in Appendix C.**

Graphical Presentation of Dose-Response Relationship

We present graphically the results of studies associating outcomes with categorical exposures (e.g., percentiles or other arbitrary categories of 25(OH)D concentration or of total calcium intake). The graphs complement the information mentioned in the tables and allow the reader to appreciate the direction of the estimated effects, even when the choice of the reference category is inconsistent across studies. The graphs do not readily convey the slope (strength) of the dose-response relationship between exposure and outcome, because the exposure categories are simply ranked and their spacing does not necessarily correspond to the actual values that they represent within a study or across studies.

Grand Summary Tables (Evidence Map)

In the beginning of the Results section, we created a grand overview table. The table details how many studies reported an outcome of interest (either as a primary or non-primary outcome) **both in the original 2009 report and in the current report** and also listed the total number of

unique studies (including systematic reviews) as each study may have provided data on more than one outcome. The number of primary studies included in each existing systematic review is also reported.

Units of Measurement

In this report, we converted serum 25(OH)D concentrations as reported by various studies as different units (i.e., ng/mL, μg/dL, μg/L and ng/dL) to nmol/L. The conversion formula is 1 ng/mL = 2.5 nmol/L. To limit the variation in the reporting of vitamin D unit (e.g., nmol, IU, μg and mg), IU was chosen as the standard unit and all other units were converted using a standard formula. The conversion formula for micrograms is 1 μg = 40 IU.

Assay Method

For 25(OH)D measurements, we present information on the assay used in our evidence tables and summary tables describing individual studies. When reported, we also recorded details on the methodology or kit used (e.g., RIA–radioimmunoassay, RIA "DiaSorin") used. Often, additional information was lacking. We did not perform any subgroup analyses based on the type of 25(OH)D assay used; **Figure 15 shows the data for the effects of vitamin D administration on serum 25(OH)D concentration as a series of bubble plots for each assay method, and Table 67 shows the assay method for the studies included in the dose response figures. In Appendix G of this update report, we provide a table of the assay methods; detailed information on the kits used, if noted; reference citations for assay methods; locations and dates of assay; precision; and reference standards, if reported, for randomized controlled trials included in both the original report and the update. In particular, we note whether studies employed reference standards such as the NIST standard or reported participating in the Vitamin D External Quality Assessment Scheme (DEQAS). Finally, in Appendix H, we stratify by assay method all summary and outcomes tables for key outcomes (defined for this report as any outcomes reported in three or more RCTs or eight or more observational studies).**

Sunlight Exposure

The original report included information on country where the study took place and its latitude (when this was meaningful), and when available, the season when serum 25(OH)D concentrations were measured. A substantial amount of vitamin D is formed in the skin in humans. The amount of vitamin D synthesized in the skin depends on a person's exposure to UV irradiation. Therefore, information on country's latitude (and season of serum 25(OH)D measurements) informs on whether different populations are likely to have similar or different amount of endogenous vitamin D production. Latitudes were extracted directly from the published reports, or extrapolated from the city or country where the study took place (by searching Google for "<county/city> latitude"). For national or international studies that spanned a wide range of latitudes (e.g., NHANES), the latitude information was summarized simply as "various." To facilitate the reader, we also provide a table with the latitudes of major cities in Central and North America (located after the **Abbreviations** table).

Primary and Secondary Outcomes

For intervention studies, we distinguished primary from secondary (or nonspecified) outcomes. Outcomes were considered primary only when they were clearly reported as such or when the outcome was used in an ad hoc sample size calculation. For observational studies, we did not separate primary from secondary outcomes. For example, many observational studies are analyses of the same well known cohorts for several different outcomes. Each of these studies may have a different "primary" outcome.

Study Quality

We summarize methodological and reporting quality of individual studies and meta-analyses in the summary tables. More details on the reporting characteristics of individual studies and systematic reviews are found in the evidence tables (Appendix C).

Peer Review and Public Commentary

Experts were invited to provide external peer review of the update report. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment. We received comments back from six reviewers and one public commenter. We have addressed all peer and public comments, revising the text as appropriate, and have documented all responses in a "disposition of comments report" that will be made available 3 months after the Agency posts the final report on the AHRQ website.

Results

Organization of the Results Section

The Results section is organized in the following way:

- Nutrient (vitamin D | calcium | combined calcium and vitamin D)
    - Outcome (e.g., growth, cardiovascular diseases)
        - Synopsis
        - Detailed presentation (depending on availability of data)
            - Findings per calcium intake level / vitamin D concentration
            - Findings per age and sex
        - Findings by life stage

The findings of the studies identified for this update report are in boldface type in the text and summary tables.

Literature Search Results

For the 2009 report, the original MEDLINE® and Cochrane Central database search for primary studies yielded 15,621 citations of EAR outcomes and 194 citations of UL outcomes. The update search for primary studies published between September, 2008 and April, 2009 yielded 918 citations. We identified 654 of these as potentially relevant and retrieved the full-text articles for further evaluation. Of these, 478 did not meet eligibility criteria (Appendix F); thus, a total of 165 primary study articles met the inclusion criteria and were included in this report (Figure 5**a**). Of the 165 primary study articles, 60 were randomized controlled trials (RCTs), 3 were nonrandomized comparative studies, and 102 were observational studies (either cohort or nested case-control studies). The publication dates of the 165 primary study articles ranged from 1980 to 2009.

The MEDLINE®, Cochrane Database of Systemic Reviews, and the Health Technology Assessments database search for systematic reviews yielded 1,746 citations. We identified 68 of these as potentially relevant and retrieved the full-text articles for further evaluation. Of these, 46 did not meet eligibility criteria. After examining the 22 qualifying systematic reviews, 11 were excluded for various reasons (Appendix D; Figure 5a).

The grand overview tables (Tables 1, 2, and 3) detailed how many studies reported an outcome (either as a primary or secondary outcome) that is of interest and also listed the total number of unique studies (including those from systematic reviews) as each study may have provided data for more than one outcome.

For this update, the original MEDLINE® and Cochrane Database searches yielded 6,154 titles for EAR and UL outcomes, combined. An additional 11 titles were identified from reference mining and hand searching, for a total of 6,165 titles and abstracts that underwent dual review. Of this 6,165, 5,058 abstracts were rejected and 1,107 went on for full text review. Of that 1,107, 10 were identified as background, 772 failed to meet inclusion criteria and were rejected, and 154 articles with 156 studies went on for detailed abstraction and are included in this report (Figure 5b). In addition, 171 systematic reviewers were looked at of which 2 were included in the update report

Figure 5a. Literature flow for the original report

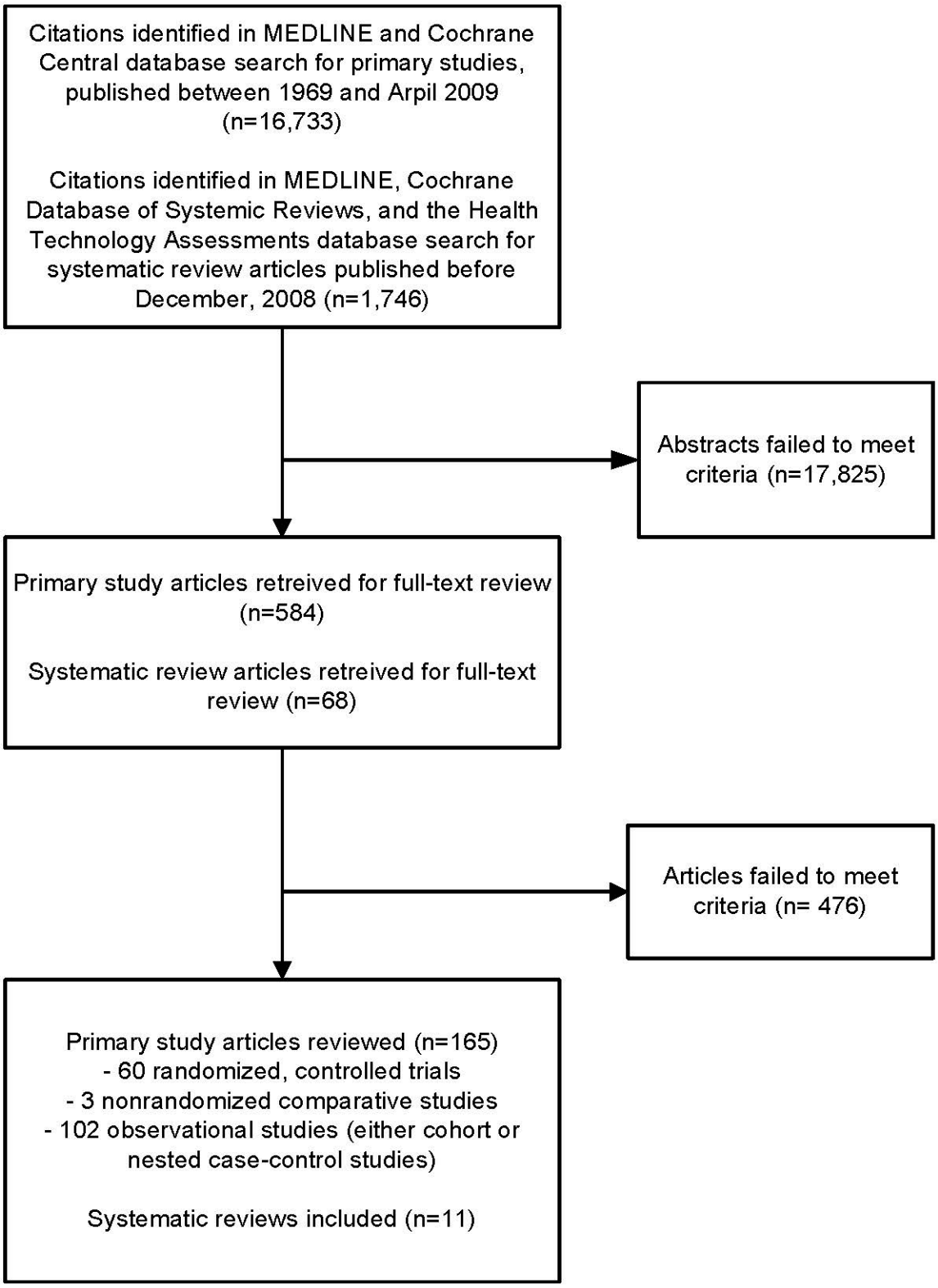


Figure 5b. Literature flow for the current report

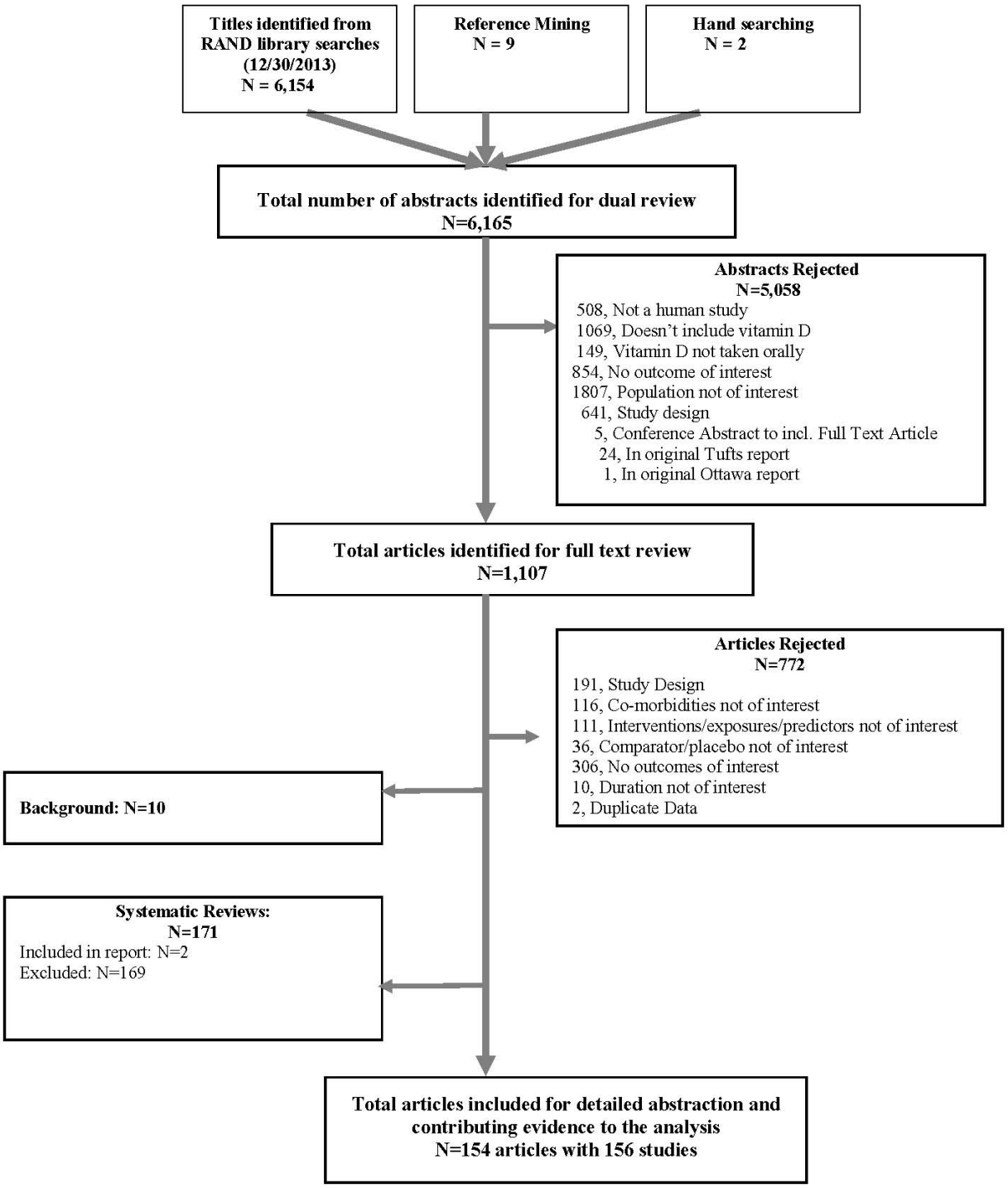


Table 1. Number of primary studies on vitamin D intake or concentration and specific health outcomes that could be applicable to certain life stages [updated for the current report]

	Growth	CVD Clinical	Body Weight (Adults)	Total Cancer	Prostate Cancer	Colorectal Cancer	Colorectal Adenoma	Breast Cancer	Breast Mammographic Density	Pancreatic Cancer	Immune Function Clinical Outcomes	Preeclampsia & Pregnancy Outcomes	All-Cause Mortality	Bone Health Clinical Outcomes	Bone Mineral Density or Content	Hypertension	Blood Pressure
0–6 mo	8										5				1		
7 mo–2 y	1										4[B]						
3–8 y											7						
9–18 y	3			1							8			2	5		
19–50 y		19	1	9	6	3		8		1	9		10	3	6	3	8
51–70 y		31	2	14	17	11	1	11		4	7		31	13	5	3	5
≥71 y		20		10	5	5		4		1	3		26	17	1	2	5
Pregnant & lactating women	16										6	9					
Postmenopause		4	1	2		1		1	2		2[B]		2	3	3	1	4
Total unique studies per outcome	**18**	**36**	**3**	**16**	**19**	**14**	**1**	**12**	**2**	**4**	**27**	**9**	**34**	**22**	**12**	**4[C]**	**13**
[Total number of RCTs per outcome]	**[10]**	**[1]**	**[3[A]]**	**[2]**	**[0]**	**[1]**	**[0]**	**[0]**	**[1]**	**[0]**	**[7]**	**[1]**	**[8]**	**[9]**	**[12[A]]**	**[0]**	**[13[A]]**
Systematic reviews (unique studies) per outcome	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (4)**	**1 (73)**		**0**	**0**

Note: Shaded cells indicate that either the eligibility criteria excluded outcomes in those life stages or the outcomes are not applicable to those life stages. Blank unshaded cells indicate no primary studies were identified in this report in those life stages.
Abbreviations: CVD = cardiovascular disease; RCT = randomized controlled trial

[A]Only RCTs were eligible for this outcome.
[B]Relationship between maternal 25(OH)D concentration and atopic eczema in infants.
[C]1 study was a combined analysis of Nurses' Health Study and Health Professionals Followup Study.

Table 2. Number of primary studies on calcium intake and specific health outcomes that could be applicable to certain life stages [not updated in the current report]

	Growth	CVD Clinical	Body Weight (Adults)	Total Cancer	Prostate Cancer	Colorectal Cancer	Colorectal Adenoma	Breast Cancer	Breast Mammographic Density	Pancreatic Cancer	Immune Function Clinical Outcomes	Preeclampsia & Pregnancy Outcomes	All-Cause Mortality	Bone Health Clinical Outcomes	Bone Mineral Density or Content	Hypertension	Blood Pressure
0–6 mo	1																
7 mo–2 y																	
3–8 y	1																
9–18 y	3																
19–50 y		2	3	1		3		1	1	1			1			5	3
51–70 y		9	5	1	12	17	6	5		2			1			4	2
≥71 y		1	1	1		1[B]				1							2
Pregnant & lactating women	1											14					
Postmenopause		1	4	1				4								1	2
Total unique studies per outcome	**3**	**11**	**8**	**3**	**12**	**21**	**6**	**6**	**1**	**2[C]**	**0**	**14**	**1**			**5[D]**	**5**
[Total number of RCTs per outcome]	**[1]**	**[0]**	**[8[A]]**	**[2]**	**[0]**	**[0]**	**[1]**	**[0]**	**[0]**	**[0]**						**[0]**	**[5[A]]**
Systematic reviews (unique studies) per outcome	**1 (17)**	**0**	**3 (41)**	**0**	**0**	**1 (2)**	**1 (2)**	**0**	**0**	**0**	**0**	**1 (12)**	**0**			**0**	**6 (64)**

Shaded cells indicate that either the eligibility criteria excluded outcomes in those life stages or the outcomes are not applicable to those life stages. Blank unshaded cells indicate no primary studies were identified in this report in those life stages.

[A]Only RCTs were eligible for this outcome.
[B]Association between total calcium intake in childhood and colorectal cancer after 65 years of followup.
[C]1 study was a combined analysis of Nurses' Health Study and Health Professionals Followup Study.
[D]6 analyses, including 2 separate analyses of NHANES I.

Table 3. Number of primary studies on combined vitamin D and calcium intake and specific health outcomes that are relevant to certain life stages [updated for the current report]

	Growth	CVD Clinical	Body Weight (Adults)	Total Cancer	Prostate Cancer	Colorectal Cancer	Colorectal Adenoma	Breast Cancer	Breast Mammographic Density	Pancreatic Cancer	Immune Function Clinical Outcomes	Preeclampsia & Pregnancy Outcomes	All-Cause Mortality	Bone Health Clinical Outcomes	Bone Mineral Density or Content	Hypertension	Blood Pressure
0–6 mo	1																
7 mo–2 y																	
3–8 y																	
9–18 y															3		
19–50 y			1											1	3		1
51–70 y		1	1	1		1	1	1		1			3	3	5	1	1
≥71 y			1	1		1		1		1			8	2	3		
Pregnant & lactating women	1											1					
Postmenopause		2	1	4		2	1	2		1			9	2	6	1	1
Total unique studies per outcome	**1**	**2[B]**	**2[B]**	**4[B]**	**0**	**2[B]**	**2[B]**	**2[B]**	**0**	**1**	**0**	**1**	**12[BC]**	**6[B]**	**11**	**1[B]**	**2[B]**
[Total number of RCTs per outcome]		**[2]**	**[2[A]]**	**[4]**		**[2]**	**[1]**	**[2]**		**[1]**			**[12]**	**[6]**	**[11[A]]**	**[1]**	**[2[A]]**
Systematic reviews (unique studies) per outcome	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1 (10[B])**	**1 (119[B])**		**0**	**0**

Shaded cells indicate that either the eligibility criteria excluded outcomes in those life stages or the outcomes are not applicable to those life stages. Blank unshaded cells indicate no primary studies were identified in this report in those life stages.

[A]Only RCTs were eligible for this outcome.
[B]Including the Women's Health Initiative (WHI) trial.
A de novo reanalysis of the 10 RCTs in a previous systematic review and one newly added trial.

Vitamin D and Health Outcomes

Vitamin D and Growth

The original report reviewed primary studies that evaluated relationships between vitamin D and growth parameters in infants and children. That topic was not updated in the current

report; only the original findings are reported here for those outcomes. **The current report did review the evidence on the outcomes of birth weight and length.**

Synopsis

For the current report, we identified five RCTs (reported in four articles) and two observational studies that evaluated intake of or exposure to vitamin D, respectively, on birth weight and/or length. One of the five RCTs found a significant association of maternal vitamin D intake from supplements with birth weight and birth length; one of the four remaining studies was not powered to measure differences in birth weight or length; the remaining three observed no difference. Of the two observational cohort studies, one observed a significant association of second trimester maternal 25(OH)D concentrations and one found no association.

In the original report, seven intervention studies and two observational studies evaluated intake of or exposure to vitamin D and growth parameters in infants and children. Two intervention studies from the same center found a significant association of maternal vitamin D intakes with infant birth weights. Study methodologies were incompletely reported in these two studies. The rest of the studies did not find a significant association between either maternal or offspring vitamin D intake and offspring's weight or height. No overall conclusions could be drawn as the studies reviewed had diverse populations and methodological approaches.

Detailed Presentation (Tables 4, 5, 6, & 7)

In the current report, five RCTs (reported in four articles)[1,42-44] reported on the effect of vitamin D supplementation during pregnancy on birth weight and/or length. Two cohort studies reported on the association between maternal serum 25(OH)D concentration and birth weight and/or length.[45,46] The number of participants in the RCTs ranged from 140 to 504; the two cohort studies followed 1,113 and 2,146 mother-infant pairs. One U.S. RCT divided 350 women who were already receiving prenatal vitamins that provided 400IU per day at 16 weeks gestation or earlier into three groups, who were given an addition 0, 1,600, or 3,600 IU vitamin D per day through the remainder of gestation; the study found no difference in birth weight among interventional arms (rated A).[1] The second study, a pseudo-RCT conducted in India, divided 140 pregnant women at 12 to 24 weeks gestation into two groups: one was administered one 1,500 microgram dose of vitamin D, and the other received two doses of 3,000 micrograms vitamin D. A group of untreated women who were 24 week pregnant or more served as the controls. Both of the treated groups gave birth to infants who were significantly heavier than the usual care group (p=0.003) (rated C, largely attributable to incomplete reporting and the fact that the study was not a truly randomized study).[43] The third RCT, the AViDD study, conducted in Bangladesh randomly divided 160 women at 26 to less than 30 weeks gestation to receive 35,000IU vitamin D per week or no supplement; no difference was seen in birth weight or length, although the study was not powered to see differences in these outcomes (rated A).[44] For the fourth and fifth studies, data from the National Institute of Child Health and Disease (NICHD) and Thrasher Research Fund Vitamin D_3 Supplementation studies, in which pregnant women were randomized to receive 0, 2000, or 4000 IU vitamin D per day in addition to their prenatal vitamins, were analyzed in combination: No differences were observed in birth weight among the groups (rated B).[42]

In the original report, six RCTs[47-53] and one nonrandomized comparative study[54] in eight publications reported on the effect of vitamin D supplementation on growth parameters in infants and children. Two cohort studies reported on the association between maternal serum 25(OH)D concentration and her offspring's growth parameters.[55,56] The number of subjects in the RCTs ranged from 19 to 200. The two cohort studies had 374 and 466 subjects, respectively. The latitudes of the studies ranged from 38º to 51º. Four studies administered vitamin D exclusively to expectant mothers during the third trimester of pregnancy. One study administered vitamin D to both the lactating mothers and her offspring. Two studies administered vitamin D only to the infants or children. Follow up ranged from delivery until 9 years. Methodological quality of two studies were rated B and seven studies were rated C. The studies were limited by such factors as incomplete reporting and small sample sizes.

Infant 0–6 Months; 7 Months–2 Years; Pregnant or Lactating Women

For the current report, five RCTs (reported in four articles) were identified that administered supplemental vitamin D to pregnant women and assessed the effect on birth weight of the offspring. One U.S. RCT divided 350 women who were already receiving prenatal vitamins that provided 400IU per day at 16 weeks gestation or earlier into three groups, who were given an addition 0, 1600, or 3600IU vitamin D per day through the remainder of gestation (assignment to the interventions was only partially random: Baseline serum 25(OH)D partly determined assignment); the study found no difference in birth weight among interventional arms.[1] A pseudo-RCT conducted in India divided 140 pregnant women at 12 to 24 weeks gestation into two groups: one was administered one 1,500 microgram dose of vitamin D, and the other received two doses of 3,000 micrograms vitamin D. A group of untreated women who were 24 week pregnant or more served as the controls. Both of the treated groups gave birth to infants who were significantly heavier than the usual care group (p=0.003).[43] A third RCT, the AViDD study, conducted in Bangladesh randomly divided 160 women at 26 to less than 30 weeks gestation to receive 35,000IU vitamin D per week or no supplement; no difference was seen in birth weight or length, although the study was not powered to see differences in these outcomes. Data from the National Institute of Child Health and Disease (NICHD) and Thrasher Research Fund Vitamin D_3 Supplementation studies, in which pregnant women were randomized to receive 0, 2000, or 4000 IU vitamin D per day in addition to their prenatal vitamins, were analyzed in combination: No differences were observed in birth weight among the intervention groups.[42] Two cohort studies assessed the effects of maternal serum 25(OH)D concentrations on birth weight in the United States. One study of 1,113 mother-infant pairs assessed the association between second trimester 25(OH)D and birth weight and the effect of race. No association was seen between quartile of maternal 25(OH)D and birth weight; but the higher risk for low birth weight among black mothers was reduced significantly when adjusted for maternal 25(OH)D (study rated A). The other cohort study, of 2,146 mother-infant pairs found a significant association between low serum 25(OH) D concentrations and lower birth weight (study rated B).[46]

In the original report, one RCT from UK administered vitamin D 1000 IU/d or placebo to 126 expectant mothers (first generation Asian immigrants) during the third trimester and found no significant difference between the infants' birth weights or birth lengths and those of the control population.[47,51] There were twice as many low birth weight infants (<2500 g) in the control group compared to the supplemented group (21.7% vs. 11.9%); however, this difference

was not significant. A study from U.S. supplemented 10 lactating mothers with vitamin D 400 IU/d and their infants with 300 IU/d for 6 months. Compared to the group where nine mothers received 6400 IU/d and their infants none, there was no significant difference in the infants' weight or length at 1 month, 4 months, and 7 months of age.[52] A study from China randomly assigned 255 newborn infants to 100, 200, or 400 IU/d of vitamin D for 6 months and reported no significant difference in weight or length among the three groups at 6 months of age.[49] One study from India randomly selected 100 expectant mothers to receive a total of 1.2 million IU of vitamin D (600,000 IU of vitamin D_2 in 7th and 8th month) during the third trimester. The newborns' birth weight was significantly increased compared to those from 100 unsupplemented expectant mothers (difference 190 g).[50] Important elements of the study methodology like randomization technique and any blinding of outcome assessors were not reported. An earlier nonrandomized comparison from the same study center involving smaller samples reported similar findings.[54] The estimated baseline mean dietary vitamin D intake in the expectant mothers from these two studies was less than 30 to 35 IU/d (the validity of these measures is unclear). An RCT from France supplemented 48 expectant mothers with either vitamin D 1000 IU/d in the third trimester or 200,000 IU one time dose at 7 month pregnancy and found no significant difference in the infants' birth weights between the two methods.[53] A cohort study from Australia analyzed the maternal serum 25(OH)D concentration in 374 women at 28–32 week gestation (geometric mean in winter 48 nmol/L; summer 69 nmol/L) and found no association with infant birth weight or length.[56] One cohort study from UK analyzed the serum 25(OH)D concentration in 466 white women in late pregnancy (~33 wk) and found the concentrations (from <30 to >75 nmol/L) were not related to their offspring's weight or height at birth, 9 months, and 9 years.[55]

9–18 Years

One RCT of vitamin D_3 (placebo, 200, or 2000 IU/d for 1 year) on girls in Lebanon aged 10–17 years found no significant difference at 1 year follow up in weight or height among the 34 girls who were premenarchal at time of enrollment.[48]

Findings by Life Stage

- **0–6 mo**

  For the current report, the results for birth weight and length are reported above. In the original report, one RCT found that supplementing expectant mothers with vitamin D 1000 IU/d during the 3rd trimester has no effect on infant birth weight or length. Another RCT found that supplementing expectant mothers with a total of 1.2 million IU of vitamin D during the 3rd trimester affected a significant increase in birth weight (+190 g). Background diet is low in vitamin D in this study. A study compared supplementing lactating mothers with vitamin D 400 IU/d and their infants 300 IU/d for 6 months with mothers supplemented with 6400 IU/d and their infants none, there was no significant difference in the infants' weight or length at 1 month, 4 months, and 7 months of age. Another study compared supplementing newborn infants with 100, 200, or 400 IU/d of vitamin D for 6 months and reported no significant difference in weight or length at 6 months of age. An RCT supplemented expectant mothers with either vitamin D 1000 IU/d during the third trimester or 200,000 IU one time dose at 7 month pregnancy and found no significant difference in the infants' birth weights between the two methods. A cohort study analyzed the maternal serum 25(OH)D concentration at 28–32 week

gestation (geometric mean in winter 48 nmol/L; summer 69 nmol/L) and found no association with infant birth weight or length. Another cohort study found that serum 25(OH)D concentration (ranged from <30 to >75 nmol/L) in late pregnancy (~33 wk) was not related to the newborn's weight or height at birth, 9 months, and 9 years.

- **7 mo–2 y**
  A cohort study found that serum 25(OH)D concentration (ranged from <30 to >75 nmol/L) in late pregnancy (~33 wk) was not related to the newborn's weight or height at birth, 9 months, and 9 years.
- **3–8 y**
  No study covered this life stage.
- **9–18 y**
  A cohort study found that serum 25(OH)D concentration (ranged from <30 to >75 nmol/L) in late pregnancy (~33 wk) was not related to the newborn's weight or height at birth, 9 months, and 9 years. One RCT of vitamin D_3 (placebo, 200, or 2000 IU/d for 1 year) on girls 10–17 years old found no significant difference at 1 year follow up in weight or height among the girls who were premenarchal at time of enrollment.
- **19–50 y**
  Not reviewed
- **51–70 y**
  Not reviewed
- **≥71 y**
  Not reviewed
- **Postmenopause**
  Not reviewed
- **Pregnant & lactating women: The results for the current study are reported above. For the original study,** one RCT found that supplementing expectant mothers with vitamin D 1000 IU/d during the 3rd trimester has no effect on infant birth weight or length. Another RCT found that supplementing expectant mothers with a total of 1.2 million IU of vitamin D during the 3rd trimester affected a significant increase in birth weight (+190 g). Background diet is low in vitamin D in this study. A study compared supplementing lactating mothers with vitamin D 400 IU/d and their infants 300 IU/d for 6 months with mothers supplemented with 6400 IU/d and their infants none, there was no significant difference in the infants' weight or length at 1 month, 4 months, and 7 months of age. An RCT supplemented expectant mothers with either vitamin D 1000 IU/d during the third trimester or 200,000 IU one time dose at 7 month pregnancy and found no significant difference in the infants' birth weights between the two methods.

Table 4. Vitamin D and growth outcomes: Characteristics of interventional studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
RCTs						
Maxwell 1981[51] Brooke 1980[47] UK (51ºN) [6793058] [6989438]	• Health status • Mean age (range/SD), y • Male (%)	pregnancy nd 0	25(OH)D at 28–32 wk: 20.1 nmol/L	Vit D 1000 IU/d 3rd trimester only	nd	First generation Asian immigrants only
Feliciano 1994[49] China (22ºN to 47ºN) [8078115]	• Health status • Mean age (range/SD), y • Male (%)	healthy term newborn nd	86% infant breastfed until 5–6 mo	Vit D 100 IU/d vs. 200 IU/d vs. 400 IU/d	nd	
El-Hajj 2006[48] Lebanon (33ºN) [16278262]	• Health status • Mean age (range/SD), y • Male (%)	healthy 13.2 (10–17) 0	25(OH)D 35 nmol/L; dietary Ca 677 mg/d	Vit D_3 200 IU/d vs. 2000 IU/d vs. placebo x 1 y	98% in placebo; 98% in low dose; 97% in high dose	7.4 h sun exposure/wk
Wagner 2006[52] Charleston, US (32ºN) [17661565]	• Health status • Mean age (range/SD), y • Male (%)	Fully lactating; <1 mo postpartum 29 0	Lactating mother's dietary Vit D 273 IU/d; dietary calcium intake: 1125 mg/d;	Mother Vit D_3 400 IU/d + infant 300 IU/d vs. mother 6400 IU/d + infant 0 IU/d	≥80% in mothers; as low as 61% for infants	78% white; 11% black; 11% Hispanic
Marya 1988[50] India (28ºN) [3243609]	• Health status • Mean age (range/SD), y • Male (%)	no pregnancy-related complications 24 0	Expectant mother's dietary Vit D 35 IU/d; calcium 429 mg/d	Mother Vit D 1.2 mil IU (total; 600,000 IU vit D_2 in 7th & 8th mo) vs. no supplement	nd	
Mallet 1986[53] France (48ºN) [3755517]	• Health status • Mean age (range/SD), y • Male (%)	pregnancy newborn nd	Ca intake 550 to 1000 mg/d in 55% of the subjects	Vit D 1000 IU/d vs. 200,000 IU 1x dose	nd	
Nonrandomized comparative study						
Marya 1981[54] India (28ºN) [7239350]	• Health status • Mean age (range/SD), y • Male (%)	no pregnancy-related complications nd 0	Expectant mother's daily milk intake <500 mL; dietary Vit D <30 IU/d	Vit D 1200 IU/d + Ca 375 mg/d (3rd trimester) or Vit D 1.2 mil IU (total; 600,000 IU in 7th & 8th mo) or no supplement	nd	

Table 4. Vitamin D and growth outcomes: Characteristics of interventional studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
New Studies						
Hollis, 2011[1] Charleston, US	• Health status • Mean age (range/SD), y • Male (%)	Healthy 27 (18–41/5.6) 0%	serum: delivered group- 59.5 23.8 nmol/L (6.0–172.5) exited group- 50.5 25.1nmol/L (6.5–120.5) vit D intake: 400 IU group- 181.6 +/- 108.4 IU/d, 2000 IU group- 195.8 +/- 135.0, 4000 IU group- 204.2 +/- 148.2 calcium intake: 400 IU group-1063.6 +/- 539.6 mg/d, 2000 IU group- 993.9 +/- 514.0 mg/d, 4000 IU group- 1073.6+/- 491.9 mg/d	Birth weight: Vit D 4000 IU vs. Vit D 2000 IU vs. Vit D 400 IU	69% (400-IU group), 68% (2000-IU group), and 69% (4000-IU group, p¼0.9)	Assignment to the interventions was only partially random: Baseline serum 25(OH)D also partly determined assignment
Kalra, 2012[43] India	• Health status • Mean age (range/SD), y • Male (%)	nd 26.7 (SD 4.0) 0%	Table 2: Group 1 – 31.7 nmol/L (14.0–57.2) Group 2– 32.0 nmol/L (14.5–45.7)	Birth weight: 3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation) vs. 1500 mg cholecalciferol (one dose 2nd trimester) Length at Birth: 3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation) vs. 1500 mg cholecalciferol (one dose 2nd trimester)	nd	

Table 4. Vitamin D and growth outcomes: Characteristics of interventional studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Roth 2013[44] Bangladesh	• Health status • Mean age (range/SD), y • Male (%)	Healthy 22.4 (SD 3.5) 0%	Serum 25(OH)D placebo: 44.0 ± 20.9 nmol/l vitamin D: 45.4 ± 18.4 nmol/l	Birth weight: 35000 IU Vit D3 3rd trimester vs. Placebo Length at birth: 35000 IU Vit D3 3rd trimester vs. Placebo	99.2 ± 2.7%
NEW Cohort study					
Wagner 2013[42] US	• Health status • Mean age (range/SD), y • Male (%)	nd 27 (18–41) 0%	61.5 nmol/L	2000 IU vit D3 vs. 4000 IU vit D3 vs. control	NR

Table 5. Vitamin D and growth outcomes: Characteristics of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted: Nutrients	Demographics	Anthropometric Measures	Medical	UV Exposure	Lifestyle	Comments
Morley 2006[56] Australia (38ºS) [16352684]	• Health status	singleton pregnancy; no disease	• Assay method	RIA	Length and weight in offspring stratified by mother's 25(OH)D	O	X	X	0	X	X	99% white; excluded dark skin or women with concealing clothing
	• Mean age (range/ SD), y	29										
	• Male (%)	0	• Season blood drawn	winter & summer								
Gale 2008[55] PAHSG UK (50ºN) [17311057]	• Health status	singleton pregnancy <17 wk	• Assay method	RIA	Length and weight in offspring stratified by mother's 25(OH)D	0	X	0	0	X	0	White only
	• Mean age (range/ SD), y	26.3										
	• Male (%)	0	• Season blood drawn	nd								
New Studies												
Burris 2012 [45] Massachusetts, US	• Health status	nd			Weight in offspring stratified by mother's 25(OH)D	0	X	X	0	X	0	
	• Mean age (range/SD), y	33 (SD 4.5)										
	• Male (%)	0%										
Gernand, 2013[46] US	• Health status	Singleton gestation			Weight in offspring stratified by mother's 25(OH)D	0	X	X	0	X	X	
	• Mean age (range/SD), y	nd										
	• Male (%)	0%										

Abbreviations: X = factor adjusted for in analysis; O = factor not adjusted for.

Table 6. Vitamin D and growth outcomes: Results of RCTs (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change (SD)	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Maxwell 1981[51] Brooke 1980[47] [6793058] [6989438]	Pregnant women & infant 0–6 mo (Asians)	Infant birth weight	2°	until delivery	Vit D 1000 IU	59	g	NA	Final 3157	3037, 3277	Diff 123	-50, 296[A]	NS	B
					Control	67		NA	3034	2909, 3159				
		Infant birth length	2°	until delivery	Vit D 1000 IU	59	cm	NA	Final 49.7	49.6, 49.8	Diff 0.2	0.1, 0.3[A]	NS	
					Control	67		NA	49.5	49.4, 49.6				
Feliciano 1994[49] [8078115]	0–6 mo	Weight gain born in spring, N. China[B]	1°	6 mo	Vit D 400 IU	12	g	nd	3745	2613, 4877	-463	-1852, 926[A]	NS	C
					Vit D 200 IU	13		nd	5296	4718, 5874	1088	96, 2080[A]	NS	
					Vit D 100 IU	17		nd	4208	3402, 5013				
		Length gain born in spring, N. China	1°	6 mo	Vit D 400 IU	12	cm	nd	18.8	17.4, 20.2	-0.5	-2.7, 1.7[A]	NS	
					Vit D 200 IU	13		nd	19	18.1, 19.9	-0.3	-2.2, 1.6[A]	NS	
					Vit D 100 IU	15		nd	19.3	17.6, 21.0				
El-Hajj 2006[48] [16278262]	9–18 y female, premenarche	Height	2°	1 y	Vit D_3 2000 IU	nd, ≤34 total	%	nd	5.60%	~4.8, 6.4[C]	~1.8%	~0.6, 3.0[A]	0.07	C
					Vit D_3 200 IU			nd	5.00%	~4.2, 5.8[C]	~1.2%	~-0.01, 2.4[A]		
					Placebo			nd	3.80%	~0.9, 6.7[C]				
		Weight	2°	1 y	Vit D_3 2000 IU	nd, ≤34 total	%	nd	18.40%	~14.7, 22.1[C]	~3.5%	~-1.3, 8.3[A]	0.25	
					Vit D_3 200 IU			nd	15.30%	~12.5, 18.1[C]	~0.4	-3.7, 4.5[A]		
					Placebo			nd	14.90%	~11.8, 18.0[C]				

Table 6 Vitamin D and growth outcomes: Results of RCTs (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change (SD)	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Wagner 2006[52] [17661565]	Lactating mothers & infant 0–6 mo; 7 mo–2 y	Infant weight[C]	1°	7 mo	Mother (400) +infant (300)	10	g	NA	Final 7600	7100, 8100	Diff -800	-2300, 700[A]	0.3	C
					Mother (6400) +infant (0)	9		NA	8400	7700, 9100				
		Infant length	1°	7 mo	Mother (400) +infant (300)	10	cm	NA	Final 65.5	64.4, 66.6	Diff -3.8	-7.8, 0.2[A]	0.06	
					Mother (6400) +infant (0)	9		NA	69.3	67.4, 71.2				
Marya 1988[50] India [3243609]	Pregnant women & infant 0–6 mo	Birth weight	1º	Delivery	Vit D 1.2 mil IU total	100	g	NA	Final 2990	2920, 3060	Diff 190	90, 290[A]	<0.001	C
					No supplement	100		NA	2800	2730, 2870				
		Birth length	2º		Vit D 1.2 mil IU total	100	cm	NA	Final 50.06	49.7, 50.4	Diff 1.6	1.1, 2.1[A]	<0.001	
					No supplement	100		NA	48.45	48.1, 48.8				
Marya 1981[54] [7239350][E]	Pregnant women & infant 0–6 mo	Birth weight	2º	Delivery	Vit D 1.2 mil IU total	20	g	NA	Final 3140	2940, 3340	Diff 410	166, 654[A]	0.001	C
					Vit D 1200 IU + 375 mg Ca (3rd trimester)	25	g	NA	Final 2890	2760, 3020	Diff 160	0, 320[A]	0.05	
					No supplement	75		NA	2730	2650, 2810				
Mallet 1986[53] France (48º N) [3755517]	Pregnant women & infant 0–6 mo	Birth weight	2°	delivery	Vit D 1000 IU	21[D]	g	NA	Final 3370 (80)		Diff 160		NS	C
					Vit D 200,000 IU 1x dose	27[D]		NA	3210 (90)					

Table 6 Vitamin D and growth outcomes: Results of RCTs (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change (SD)	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
NEW Studies														
Hollis 2011[1]	Pregnant or lactating women	Birth weight	2°	Delivery	Vit D 4000 IU	117	g	NR	Final 3284.6	3175.2, 3394.0	+62.8	-103.4, 229.0	0.23	A
					Vit D 2000 IU	122			Final 3360.1	3255.2, 3465.0	+138.3	-24.4, 301.0		
					Vit D 400 IU	111			Final 3221.8	3094.9, 3348.8				
Kalra 2012[43]	Pregnant or lactating women between 12–24 weeks gestation	Birth weight	1°	Delivery	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)	35	kg	NR	Final 3.03	1.71, 4.35	-0.05	-1.92, 1.82	0.96	C
					1500 mg cholecalciferol (one dose 2nd trimester)	36	kg		Final 3.08	1.71, 4.45				
		Length at birth	1°	Delivery	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)	35	cm	NR	Final 50.1	49.8, 50.4	-0.2	-0.6, 0.2	0.35	
					1500 mg cholecalciferol (one dose 2nd trimester)	36	cm		Final 50.3	50.0, 50.6				
Roth 2013[44]		Birth weight	2°	Delivery	35000 IU Vit D^3 3rd trimester	73	g	NR	Final 2802	2675, 2929	+14	-138, 166	0.86	A
					Placebo	74	g		Final 2788	2700, 2876				
		Length at birth	2°	Delivery	35000 IU Vit D^3 3rd trimester	73	cm	NR	Final 48.2	47.6, 48.8	+0.2	-0.5, 0.9	0.55	
					Placebo	74	cm		Final 48	47.5, 48.5				
Wagner 2013[42]		neonatal birth weight	1°		2000 IU vit D^3	201	g	NR	Final 3382	sd=759	+149	-21, 319	0.09	B
					4000 IU vit D^3	193			Final 3231	sd=632	-2	-154, 150	0.98	
					control	110			Final 3233	sd=668				

Note: Outcomes cells are shaded for the Control rows.
[A]Estimated from available data.
[B]See Table 1 in original paper for complete results stratified by North vs. South China and birth in spring vs. fall.
[C]See Table 3 in original paper for results on 1 mo and 4 mo.
[D]Estimated from number of mothers; number of infants not reported.
[E]This is not an RCT; the supplemented groups were randomized, but not the control (non-supplemented group); data from comparisons between the supplemented groups not reported.

Table 7. Vitamin D and growth outcomes: Results of cohort studies (updated from original report)

Author Year Study Name PMID	Life Stage	Outcome (n/N; Incidence)	Followup Duration	Maternal 25(OH)D Concentration, nmol/L	No. in Category	Final Value	Final SD	P Value	Study Quality
Morley 2006[56] Australia [16352684]	Pregnant women; infant 0–6 mo	Birth weight (N=374)	Delivery	<28 at 28–32 wk	27	3397 g	57	NS	B
				≥28 at 28–32 wk	347	3555	52		
		Birth length (N=374)	Delivery	<28 at 28–32 wk	27	49.8 cm	2.7	NS	
				≥28 at 28–32 wk	347	50.4	2.4		

Table 7 Vitamin D and growth outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name PMID	Life Stage	Outcome (n/N; Incidence)	Followup Duration	Maternal 25(OH)D Concentration, nmol/L	No. in Category	Final Value	Final SD	P Value	Study Quality
Gale 2008[55] PAHSG, UK [17311057]	Pregnant women; infant 0–6 mo	Birth weight (N=466)	Delivery	<30 (Quartile)	nd	3.38 kg	0.46	0.25[A]	C
				30–50	nd	3.4	0.56		
				50–75	nd	3.49	1.57		
				>75	nd	3.43	0.51		
		Weight at 9 mo (N=440)	9 mo	<30	nd	15.9	1.14	0.58	
				30–50	nd	15.8	1.26		
				50–75	nd	16.1	1.34		
				>75	nd	15.9	1.09		
		Weight at 9 y (N=178)	9 y	<30	nd	27.4 kg	1.19	0.1	
				30–50	nd	29.4	1.21		
				50–75	nd	30	1.2		
				>75	nd	29.3	1.19		
	Pregnant women; infant 0–6 mo	Birth length (N=466)	Delivery	<30	nd	50 cm	1.83	0.15	
				30–50	nd	50	2.29		
				50–75	nd	50.5	2.25		
				>75	nd	50.1	2.09		
		Length at 9 mo (N=440)	9 mo	<30	nd	71.2 cm	2.85	0.86	
				30–50	nd	71.4	2.6		
				50–75	nd	71.7	2.89		
				>75	nd	71.1	2.67		
		Height at 9 y (N=178)	9 y	<30	nd	129.6 cm	5.88	0.19	
				30–50	nd	131.5	6.66		
				50–75	nd	131.8	5.09		
				>75	nd	130.6	6.45		

Table 7. Vitamin D and growth outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name PMID	Life Stage	Outcome (n/N; Incidence)	Followup Duration	Maternal 25(OH)D Concentration, nmol/L	No. in Category	Final Value	Final SD	P Value	Study Quality
NEW Studies									
Burris 2012[45]	Pregnant or lactating women	Birth weight	Delivery	<25				ND	
				25–50					
				50–75					
				≥75					
Gernand 2013[46]	singleton gestation	Birth weight	Delivery	<37.5				0.014	
				≥37.5					

Vitamin D and Cardiovascular Disease

Synopsis

One qualified systematic review of prospective studies identified for the current report found a significant association between low serum 25(OH)D concentrations and a number of clinical cardiovascular outcomes, including total cardiovascular disease, coronary heart disease, cardiovascular disease mortality, and stroke. No RCTs identified for the current report evaluated the effects of vitamin D on clinical cardiovascular disease outcomes. Observational studies identified for the current report found mixed associations between 25(OH)D and total cardiovascular events, cardiovascular death, myocardial infarction, stroke, and fatal stroke. Significant associations were found between progressively lower 25(OH)D concentration and increased risk for cardiovascular events in two studies of people approximately 40 to 75 years old. No significant associations were found between serum 25(OH)D concentrations and cardiovascular death, myocardial infarction, or stroke in one study each.

For the original report, no qualified systematic reviews have evaluated the association between vitamin D intake or serum 25(OH)D concentrations and incidence of hypertension. One RCT of almost 2700 elderly British who received either vitamin D_3 100,000 IU every 4 months or placebo for 5 years found no statistically significant difference in event rates for various cardiovascular outcomes, including total events and cardiovascular deaths. No effects were also found in subgroup analyses of men and women. Three cohort and one nested case-control studies have analyzed the association between serum 25(OH)D concentrations and cardiovascular outcomes (cardiovascular events, nonfatal myocardial infarction or fatal coronary heart disease, cardiovascular death, myocardial infarction, and stroke). Significant associations were found between progressively lower 25(OH)D concentration and progressively increased risk of cardiovascular events in two studies of people approximately 40 to 75 years old. No significant associations were found between serum 25(OH)D concentrations and cardiovascular death, myocardial infarction, or stroke in one study each.

Detailed Presentation (Tables 8, 9, 10,and 11a-b; Figures 6a-h)

Total Cardiovascular Events (Figure 6a, b, e, and h)

One high-quality systematic review[57] that included 17 studies, 16 of which were included in the original report or the current report (the remaining study was excluded from the current report) found a significant association between lower serum 25(OH)D concentrations and increased risk for total cardiovascular disease and coronary heart disease risks.

Six prospective cohort studies evaluated the association between serum 25(OH)D concentrations and the incidence of total cardiovascular events, ranging from 4.4 years to 14.4 years followup. Three of these studies found no significant association between levels of serum 25(OH)D and risk for a cardiovascular event (two rated A, one rated B).[58-60] One study, the German MONICA/KORA cohort study, with a mean followup of 11 years, found significantly decreased risks of total cardiovascular events for both men and women, with a larger effect in women (rated A).[61] Another study, the U.S. MESA study, found an association of serum 25(OH)D with decreased risk of CHD among Caucasians and Chinese

participants but not among Black or Hispanic participants (rated A).[62] The German ESTHER cohort study found that serum 25(OH)D concentrations of less than 75nmol/L were associated with an increased risk for all cardiovascular events (rated B).[63]

Two nested case-control studies were identified. One nested case-control study within the Tehran Lipid and Glucose Study with 5.7 years followup found a significantly increased risk for total cardiovascular events for individuals in the lowest tertile of 25(OH)D concentrations compared with the two higher tertiles (rated B).[64] A study nested within the multi-country EPIC study found no association of serum 25(OH)D with total CV events in the fully adjusted model (rated A).[65]

In the original report, total cardiovascular events were evaluated by an RCT,[66] the Framingham Offspring Study (FOS),[67] and a nested case-control study derived from the Health Professionals Followup Study (HPFS).[68] The RCT found no significant effect of vitamin D; both cohort studies found significant associations between lower serum 25(OH)D concentrations and increased rates of outcomes.

The RCT randomized almost 2700 elderly participants (65–85 years) from the general population in Ipswich, UK (52° N) to vitamin D_3 100,000 IU every 4 months or placebo.[66] After 5 years, 36 percent of the participants had a cardiac or cerebrovascular event, but there was no statistically significant difference between those taking vitamin D and those taking placebo. Similar results were found in subgroups of men and women. The RCT was rated quality B primarily due to inadequate verification of outcomes.

The FOS cohort evaluated 1739 men and women with no history of cardiovascular disease and a mean age of 59 years (based on the standard deviation, with an approximate rage of 41 to 77 years).[67] After 5.4 years, 6.9 percent had a cardiovascular event (including myocardial infarction, coronary insufficiency, angina, stroke, transient ischemic attack, claudication, and heart failure). Overall, the methodological quality of the study was A; though their secondary analysis of three categories of serum 25(OH)D concentrations (as opposed to two categories) was rated C due to incomplete reporting and lack of adjustment for important variables including season of blood draw. In their primary analysis, people with serum 25(OH)D concentrations less than 37.5 nmol/L were 70 percent more likely (P=0.02) to have a cardiovascular event. In their secondary analysis, those with 25(OH)D concentrations between 25 and 37.5 nmol/L were about 50 percent more likely (P=0.01) to have an event than those with higher concentrations. Furthermore, a multivariable analysis of continuous 25(OH)D concentrations suggested increased likelihoods of cardiovascular events in those with 25(OH)D concentrations below approximately 50 to 55 nmol/L.

In a nested case-control study of the HPFS, 454 men 40 to 75 years old with no cardiovascular history who had a nonfatal myocardial infarction or coronary heart disease death over a 10 year period were matched with 1354 controls.[68] The methodological quality of the analysis was A, although due to limitations on analyzable serum, the investigators had to use a case-control analysis instead of a complete analysis of all eligible men in the HPFS. Across four categories of men based on their serum 25(OH)D concentrations, lower concentrations were significantly associated with increased cardiovascular events (trend across categories P=0.02). Compared with men who had 25(OH)D concentrations above 75 nmol/L, those with 25(OH)D concentrations 56 to 75 nmol/L had an adjusted relative risk (RR) of 1.6 (95% CI 1.1, 2.3), those with 25(OH)D 37.5 to 56 nmol/L had an RR of 1.4 (95% CI 0.96, 2.1), and those with 25(OH)D below 37.5 nmol/L had an RR of 2.1 (95% CI 1.2, 3.5).

Cardiovascular Death (Figures 6c and 6d)

Sixteen prospective studies and one nested case control study that examined the association between serum 25(OH)D and risk for cardiovascular death (including fatal myocardial infarction, sudden cardiac death, and coronary disease death) were identified for the current report. Seven prospective cohort studies (reported in eight articles) and the nested case control studies, with followups ranging from 7.3 to 29 years (one study did not report length of followup and one, an analysis of NHANES data, reported follow up in person years), observed an increased risk for cardiovascular death for those with the lowest serum 25(OH)D concentrations compared with the highest (three rated A, six rated B).[63,69-76]

The study by Eaton, which followed a subsample of the Women's Health Initiative participants, found an association among women with normal waist to hip ratios but not among women with abdominal obesity (rated A).[70]

The study by Signorello observed the association among both African American and non-African American participants (rated A).[74] A study by Fiscella of 15,363 adult participants in NHANES assessed differences between African Americans and whites and found a higher risk for cardiovascular death among blacks than whites that disappeared when adjusted for the lower serum 25(OH)D levels in blacks (rated A).[71]

The Whitehall study, reported by Tomson, observed a strong inverse association among elderly men between serum 25(OH)D and risk for cardiovascular death, at a median of 13 years' followup (rated B).[75] The ESTHER study reported a strong inverse association among men and women at two followup times (4.5 and 9.2 years)(both rated B).[63,76]

The remaining 9 cohort studies, including the Octabaix 3-Year Followup study of the oldest old,[77] found no association between serum 25(OH)D concentrations and risk for cardiovascular death four A, five B).[58,78-84]

In the original report, the British RCT of vitamin $D_3$100,000 IU every 4 months versus placebo analyzed cardiovascular death as a primary outcome; 8 percent of the participants had cardiovascular deaths within 5 years.[66] Fewer people taking vitamin D_3 supplements had cardiovascular deaths (RR = 0.84), but this finding was not statistically significant (95% CI 0.65, 1.10). Similar results were found in subgroups of men and women.

An analysis of NHANES III (methodological quality C) evaluated cardiovascular death (due to hypertensive disease, ischemic heart disease, arrhythmia, heart failure, cerebrovascular disease, atherosclerosis or other disease of the arteries) in over 13,000 men and women regardless of baseline medical history.[85] During almost 9 years of follow up, 5.8 percent had a cardiovascular death. The analysis compared four categories of serum 25(OH)D concentrations ranging from less than 44.5 nmol/L to more than 80 nmol/L. No significant association was found between serum 25(OH)D concentration and cardiovascular death.

Ischemic Heart Disease (Figure 6a and b)

Three prospective cohort studies (reported in two articles) identified for the current report assessed the association between serum 25(OH)D concentrations and incident ischemic heart disease. These studies, one with a 10-year follow up and one with a 29-year follow up, found no significant difference in risk for nonfatal ischemic heart disease across four quartiles of serum 25(OH)D concentrations (both rated B).[69,86]

The RCT evaluated total ischemic heart disease.[66] In this elderly British population, 17% had an ischemic heart disease event; no effect of vitamin D_3 supplementation was found. Similar results were found in subgroups of men and women.

Ischemic Heart Disease Death (Figure 6c and d)

The pooled results of two population-based studies reported in an article identified for the current report observed an association of serum 25(OH)D with death from ischemic heart disease(rated B).[86]

An RCT identified for the original report evaluated total ischemic heart disease death as a primary outcome.[66] In the trial, 3.4% had an ischemic heart disease event; no effect of vitamin D_3 supplementation was found (RR = 0.84 [95% CI 0.56, 1.27]). Similar results were found in subgroups of men and women.

Myocardial Infarction (Figure 6e)

Five prospective cohort studies identified for the current report assessed the association between serum 25(OH)D concentration and risk for myocardial infarction. Four of the studies found no association (two rated A, two rated B).[58,69,87,88]A nested case control study within the EPIC study with a mean follow up time of 7.6 years found an association between serum 25(OH)D and myocardial infarction when the outcomes were adjusted only for sex and BMI but no association with a model that adjusted for various lifestyle factors as well (rated A).[65] One cohort study that followed 2,312 older adults with no history of disease at baseline for 14 years found, after adjustment, that each 25nmol/L decrease in 25-OHD concentration was associated with a 25 percent greater (95% CI: 8% to 44% greater) relative hazard of myocardial infarction.[81]

In one small analysis, 755 elderly (age 65 to 99 years) Finnish men and women, regardless of cardiovascular history, were evaluated on the basis of myocardial infarction (methodological quality C due to lack of reporting of relevant data including information on the serum 25(OH)D or $1,25(OH)_2D$ concentrations within the tertiles).[89] During 10 years of follow up, 17 percent of the participants had a myocardial infarction. Both analyses of serum 25(OH)D and $1,25(OH)_2D$ concentrations found no significant association with risk of myocardial infarction.

Stroke (Figure 6f)

Seven prospective cohort studies identified for the current report assessed the association between serum 25(OH)D concentration and risk for stroke or transient ischemic attack. Three of the studies (followup ranging from 17 to 29 years) found a significantly increased risk for stroke or TIA for those with the lowest or lower serum 25(OH)D concentrations compared with those with the highest or higher concentrations, respectively (two rated B, one rated A),[69,88,90] although for the women in the Nurses' Health Study,[90] the difference was relatively small. The remaining four studies, with followup of 5 to 13 years, found no difference (two rated A, two rated B).[58,63,86,91]

One nested case control study within the EPIC population study, which had a followup of 7.6 years, reported a small j-shaped association of serum 25(OH)D with risk for stroke (rated A).[65]

The RCT **identified for the original report** evaluated total cerebrovascular disease.[66] In this elderly British population, 7.7% had a cerebrovascular event; no effect of vitamin D_3 supplementation was found. Similar results were found in subgroups of men and women.

Stroke was evaluated in the same small Finnish study. During 10 years of follow up, 9.3 percent of the participants had a stroke. Both analyses of serum 25(OH)D and 1,25$(OH)_2$D concentrations found no significant association with risk of stroke.

Cerebrovascular Death (Figure 6g)

Three prospective cohort studies identified for the current report assessed the association between serum 25(OH)D concentrations and risk for fatal stroke or cerebrovascular death.[63,82,83] One study, with a median followup of 27 years, found an increased risk for the lowest quintile of 25(OH)D concentration compared with the highest (rated A).[82] The other two studies, with mean followup of 9 and 24 years, found no significant association between serum 25(OH)D concentration and risk for fatal stroke or cerebrovascular death for either men or women both rated B).[63,83]

The RCT **identified for the original report** evaluated cerebrovascular disease death as a primary outcome.[66] In the trial, 2.0% had a fatal stroke; no effect of vitamin D_3 supplementation was found. Similar results were found in subgroups of men and women.

Findings per Vitamin D Concentration

The RCT **identified in the original study** compared vitamin D_3 supplementation 100,000 IU every 4 months with placebo, but found no effect on cardiovascular outcomes. Two cohort studies found a significant association between higher serum 25(OH)D concentrations and lower risk of combined cardiovascular events. Both found that those people in the highest 25(OH)D category analyzed within each study had the lowest risk. The FOS used a maximum threshold of 37.5 nmol/L; the HPFS used a maximum threshold of 75 nmol/L. The FOS provided a graphic representation of a multivariable regression of continuous 25(OH)D concentrations (Figure 2 in the study).[67] The risk of cardiovascular events rose below 37 to 50 nmol/L serum 25(OH)D concentration. The Finnish cohort did not report the range of serum 25(OH)D and 1,25$(OH)_2$D concentrations.[89]

Findings per Age and Sex

For the observational studies identified for the current report, differences were similar among men and women.

The single RCT **identified for the original report** included elderly people from the general population. No effects on various cardiovascular events were found. Subgroup analyses of men and women yielded similar findings. The four cohort studies included adults across the full age range. Three of the cohorts included about half men and women; one included only men. None evaluated potential differences in associations based on age or sex, but no differences were evident across studies.

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed

- **9–18 y**
  Not reviewed
- **19–50 y**
  For cardiovascular events, only a minority of evaluated participants were within this life stage (almost all above 40 years). The NHANES III study, which found no association between serum 25(OH)D concentration and cardiovascular death, included largely people within this life stage.
- **51–70 y**
  The majority of people investigated for the association between serum 25(OH)D concentration and cardiovascular events were within this life stage. Significant associations were found between lower serum 25(OH)D concentrations and increased rates of cardiovascular events, across a range of 25(OH)D concentrations. The NHANES III study likely included many people within this life stage; no association was found with cardiovascular death **in the original report; an analysis of a larger population identified for the current report found an association, as did a European population-based study.**
- **≥71 y**
  A number of new studies identified for the current report included a predominance of participants within this age group. Vitamin D supplementation and exposure were not consistently associated with cardiovascular outcomes in these studies. The majority of participants in the British RCT **identified for the original report** included men and women within this age group. Vitamin D supplementation was not found to have an effect on cardiovascular outcomes. Among the cohort studies, only the small Finnish study adequately evaluated people within this life stage. No significant associations were found between serum 25(OH)D or 1,25$(OH)_2$D concentrations and either myocardial infarction or stroke, however, the absolute concentrations were not reported.
- **Postmenopause**
  In the original report, only the RCT provided data on a subgroup that included only postmenopausal women: No effect of vitamin D_3 supplementation was found. **For the current report, a post hoc assessment of a sample of WHI participants found an increased risk for cardiovascular death with decreasing serum 25(OH)D among normal weight postmenopausal women but not women with abdominal obesity.**[70]
- **Pregnant & lactating women**
  Not reviewed

Table 8. Vitamin D and cardiovascular outcomes: Characteristics of RCTs [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Trivedi 2003[66] Ipswich, UK (52°N) [12609940]	• Health status • Mean age (range), y • Male (%)	General population 75 (65–85) 76%	742 mg/day (at 4 years, no difference by treatment allocation)	Vit D_3 100,000 IU vs. placebo every 4 months	76% with at least 80% compliance; 66% at last dose (80% if excluding deaths)	

Table 9. Vitamin D and cardiovascular outcomes: Results of RCTs [no new studies in the current report]

Author Year Study Name [PMID]	Age Range, Sex (Subgroup)	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Trivedi 2003[66] [12609940]	65–85 y, Both	CVD, total	2°	5 y	Vit D_3 100,000 IU every 4 mo	477	1345	Age adj RR (Vit D/ Placebo)	0.90[A]	0.77, 1.06	0.22	B
					Placebo	503	1341					
		IHD, total	2°		Vit D_3	224	1345	Age adj RR (Vit D/ Placebo)	0.94[A]	0.77, 1.15	0.57	
					Placebo	233	1341					
		CeVD, total	2°		Vit D_3	105	1345	Age adj RR (Vit D/ Placebo)	1.02[A]	0.77, 1.36	0.87	
					Placebo	101	1341					
		CVD death	1°		Vit D_3	101	1345	Age adj RR (Vit D/ Placebo)	0.84[A]	0.65, 1.10	0.20	
					Placebo	117	1341					
		IHD death	1°		Vit D_3	42	1345	Age adj RR (Vit D/ Placebo)	0.84[A]	0.56, 1.27	0.41	
					Placebo	49	1341					
		CeVD death	1°		Vit D_3	28	1345	Age adj RR (Vit D/ Placebo)	1.04[A]	0.61, 1.20	0.89	
					Placebo	26	1341					

Note: Outcomes cells are shaded for the Control rows.
Similar results for subgroups of men and women

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted: Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	Specific CVD Outcomes
Wang 2008[67] Framingham Offspring Framingham, MA (mostly) (42°N) [18180395]	• Health status • Mean age (SD), y • Male (%)	No CVD 59 (9) 45	• Assay method • Season blood drawn	RIA (DiaSorin) All	Outcome stratified by 2 or 3 categories	X[A]	X	X	X	X[A]	X	CVD event
Giovannucci 2008[68] HPFS US (various) [18541825]	• Health status • Mean age (range), y • Male (%)	No CVD 64 (40-75) 100	• Dietary assessment method • Internal validation? (y/n)	RIA (Hollis 1993) All	Outcome stratified by 4 categories[B]	X	X	X	X	X	X	Nonfatal MI or fatal CHD
Melamed 2008[85] NHANES III US (various) [18695076]	• Health status • Mean age (range), y • Male (%)	Any 45 (≥20) 46	• Assay method • Season blood drawn	RIA (DiaSorin) All (even distribution)	Outcome stratified by 4 categories	X	X	X	X	X	X	CVD death
Marniemi 2005[89] Turku, Finland (60°N) [15955467]	• Health status • Mean age (range), y • Male (%)	Any 79 (65-99) 48	• Assay method • Season blood drawn	RIA (Incstar) All	Outcome stratified by tertiles		X				X	MI Stroke

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Specific CVD Outcomes
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
New Studies:											
Bolland, 2010[58] New Zealand	• Health status • Mean age (SD), y • Male (%)	Healthy Post-menopausal 74 (SD 4.2) 0%		Outcome stratified by 2 categories		X	X	X		X	MI Stroke MI, Stroke, or sudden death TIA Congestive heart failure Death
Brondum-Jacobsen, 2012[69] Copenhagen, Denmark	• Health status • Mean age (range), y • Male (%)	nd 57 (49–66) 44%		Outcome stratified by 4 categories		X	X	X	X	X	Nonfatal ischemic heart disease Nonfatal MI Fatal ischemic heart disease/MI
Brondum-Jacobsen, 2013[92] Copenhagen, Denmark	• Health status • Mean age (range), y • Male (%)	nd 56 (48–65) 44%		Outcome stratified by 4 categories		X	X	X	X	X	Ischemic stroke

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Specific CVD Outcomes
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
deBoer, 2012[87] US (various)	• Health status nd • Mean age (SD), y 74 (SD 4.6) • Male (%) 30%		Outcome stratified by 2 categories		X	X			X	MI
Deo, 2011[78] Cardiovascular Health Study US (various)	• Health status nd • Mean age (SD), y 74 (SD 4) • Male (%) 30%		Outcome stratified by 2 categories		X	X	X	X	X	Sudden Cardiac Death
Eaton, 2011[70] US (various)	• Health status nd • Mean age (SD), y 65.1 (7.6) • Male (%) 0%		Outcome stratified by 4 categories			X	X	X	X	Cardiovascular Disease Mortality
Fiscella, 2010[71] NHANES-III nd	• Health status nd • Mean age, y 43.64 • Male (%) 48%		Outcome stratified by 2 or 4 categories		X	X	X	X	X	Cardiovascular Death

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Specific CVD Outcomes
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Ginde, 2009[72] US (various)	• Health status nd • Mean age (SD), y 73 (0.2) • Male (%) 44%		Outcome stratified by 5 categories		X	X	X	X	X	Cardiovascular Death
Hutchinson, 2010[79] Tromso Tromso, Norway	• Health Status nd • Mean age (SD), y nd • Male (%) nd		Outcome stratified by 4 categories		X	X	X		X	CVD Mortality
Jassal, 2010[80] San Diego, CA	• Health status nd • Mean age (SD), y 74 (SD 10) • Male (%) 38%		Outcome stratified by 2 categories				X			Cardiovascular Mortality
Karakas, 2013[61] MONICA/KORA Augsburg case-cohort study	• Health status Healthy • Mean age (SD), y 51.9 (SD 0.42) Range: 35–74 • Male (%) 75.5%		Outcome stratified by 3 categories		X			X		Coronary Heart Disease

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Specific CVD Outcomes
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Kestenbaum, 2011[81] CHS US (various)	• Health status nd • Mean age (SD), y 73 (SD 4) • Male (%) 42%		Outcome stratified by 4 categories							Cardiovascular Mortality Incident heart mortality Incident myocardial infarction
Kilkkinen, 2009[82] Finland	• Health status nd • Mean age (SD), y 49.4 (SD 13.6) • Male (%) 45.3%		Outcomes stratified by 5 categories		X		X			Cardiovascular Death Cerebrovascular Death Coronary Disease Death
Lin, 2012[83] Linxian, China	• Health status Healthy, Hypertension 27% • Mean age (SD), y 56.5 (SD 7.9) • Male (%) 55%		Outcome stratified by 3 categories		X	X	X		X	Cerebrovascular Death Cardiovascular Death
Messenger 2012[59] MrOS US (various)	• Health status nd • Mean age (SD), y 76.1 (SD 5.6) • Male (%) 100%		Outcome stratified by 4 categories		X					Cardiovascular disease (CHD & CVA)

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Specific CVD Outcomes
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Michaelsson 2010[84] Uppsala, Sweden	• Health status • Mean age (SD), y • Male (%)	More than 1/3 being treated for hypertension 71 (SD 0.6) 100%		Outcome stratified by 3 categories	X	X	X	X	X	X	Cardiovascular mortality
Prentice 2013[2] WHI US (various)	• Health status • Mean age (SD), y • Male (%)	Post-menopausal **50–54**: 14.2%; **55–59**: 22.8%; **60–69**: 45.5%; **70–79**: 17.5% 0%		Outcome stratified by 2 categories	X	X					MI Coronary heart disease Total heart disease Stroke Total cardiovascular disease
Schierbeck, 2012[88] Danish Osteoporosis Prevention Study Denmark	• Health status • Mean age (SD), y • Male (%)	Post-menopausal 50 (SD 2.8) 0%		Outcome stratified by 2 categories		X	X			X	Heart failure Myocardial Infarction Stroke

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Specific CVD Outcomes
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Signorello, 2010[74] US	• Health status • Mean age (SD), y • Male (%)	nd nd (nd) nd	Outcome stratified by 4 categories			X			X	Circulatory disease death
Sun, 2012[90] Nurses' Health Study US (multiple)	• Health status • Mean age (SD), y • Male (%)	nd 60.8 (5.9) 0%	Outcome stratified by 3 categories							Ischemic stroke
Welsh 2012[60] MIDSPAN Family Study UK	• Health status • Mean age (SD), y • Male (%)	Vitamin D deficient/depleted Vitamin D not deficient 45.2 (6.2) 46%	Outcome stratified by 4 categories	X	X	X	X	X	X	Cardiovascular event
Formiga 2014[77] Octabaix Spain	• Health status • Mean age • Male (%)	Oldest old 85 39.4%	Outcome stratified by 4 categories		X		X			Cardiovascular mortality

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Specific CVD Outcomes
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Tomson 2013[75] Whitehall study London, UK	• Health status • Mean age • Male (%)	self-reported health good/excellent 77.4% 76.9 (SD 4.9) 100%		Outcome stratified by 4 categories			X	X		X	Death, ischemic heart disease Death, stroke Death, other vascular Death, all vascular
Skaaby 2013[86] Monica10 and Inter99 Denmark	• Health status • Mean age • Male (%)	NR Monica 10: 55.4 (41–72.8) Inter99: 46.1(29.7–61.3) 50.2%		Outcome stratified by 4 categories		X		X	X	X	Ischemic Heart Disease Stroke
Schottker 2013[76] ESTHER Germany	• Health status • Mean age • Male (%)	NR 62 (SD 6.5) 43.8%		Outcome stratified by 3 categories		X		X	X	X	CVD mortality
Robinson-Cohen 2013[62] MESA US	• Health status • Mean age • Male (%)	NR 63.3 (SD 10.2) 47%		Outcome stratified by 4 categories	X	X	X	X		X	Incident coronary heart disease events

Table 10. Vitamin D and cardiovascular outcomes: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Specific CVD Outcomes
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Perna 2013[63] ESTHER Saarland, Germany	• Health status • Mean age • Male (%)	46.3% hypertension NR (range 50–74) 40.7%		Outcome stratified by 4 categories	X	X	X	X	X	X	Total CVD Nonfatal CVD Fatal CVD Total CHD Nonfatal CHD Fatal CHD Total Stroke Nonfatal Stroke Fatal Stroke
Kuhn 2013[65] EPIC-Germany Heidelberg, Potsdam	• Health status • Mean age • Male (%)	NR NR		Outcome stratified by 4 categories		X	X		X	X	Myocardial Infarction Stroke CVD as composite endpoint
Brodin 2013[91] Tromso study Norway	• Health status • Mean age • Male (%)	NR 62 (SD 10) 37%		Outcome stratified by 5 categories		X	X			X	Total Venous Thromboembolism

[A]Not in 3-category analysis
[B]Case-control study

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report)

Author Year Study Name [PMID]	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
CVD Events											
Both Sexes											
Wang 2008[67]					<37.5	50	481	1.7	1.08, 2.67*	0.02[A]	A
	Mean (SD)	CVD event (120/1739; 0.069)	5.4 y	25(OH)D	≥37.5	70	1258	**1**	**Reference**		
Framingham Offspring	59 (9), Both				<25	nd	nd	1.8	1.05, 3.08*	0.01	C
					25–37.5	nd	nd	1.53	1.00, 2.36*		
[18180395]					≥37.5	70	1258	**1**	**Reference**		
Men											
Giovannucci 2008[68]					≤37.5	63	150	2.09	1.24, 3.54	0.02[BC]	A
	40–75 y, Men	Nonfatal MI or fatal CHD (454 cases; 1354 controls)	10 y	25(OH)D	37.5–56.25	156	463	1.43	0.96, 2.13		
HPFS					56.25–75	165	464	1.6	1.10, 2.32		
[18541825]					>75	70	277	**1**	**Reference**		
CVD Death											
Both Sexes											
Melamed 2008[85]					<44.5	nd	nd	1.2	0.87, 1.64	nd	C
	≥20 y, Both	CVD death (777/13,331; 0.058)	8.7 y	25(OH)D	44.5–60.75	nd	nd	0.88	0.69, 1.14		
NHANES III					60.75–80.25	nd	nd	0.83	0.65, 1.07		
[18695076]					>80.25	nd	nd	**1**	**Reference**		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Myocardial Infarction											
Both Sexes											
Marniemi 2005[89] [15955467]	65–99 y, Both	MI (130/755; 0.172)	10 y	25(OH)D	nd	nd	~252	**1**	**Reference**	nd	C
					nd	nd	~252	0.99	0.64, 1.53		
					nd	nd	~252	0.77	0.47, 1.27		
				$1,25(OH)_2D$	nd	nd	~252	**1**	**Reference**	nd	
					nd	nd	~252	1.05	0.68, 1.62		
					nd	nd	~252	0.82	0.52, 1.30		
Stroke											
Both Sexes											
Marniemi 2005[89] [15955467]	65–99 y, Both	Stroke (70/755; 0.093)	10 y	25(OH)D	nd	nd	~252	**1**	**Reference**	nd	C
					nd	nd	~252	1.13	0.62, 2.05		
					nd	nd	~252	1	0.51, 1.94		
				$1,25(OH)_2D$	nd	nd	~252	**1**	**Reference**	nd	
					nd	nd	~252	0.63	0.37, 1.09		
					nd	nd	~252	0.41	0.22, 0.77*		
NEW Studies											
Bolland 2010[58] New Zealand		Primary–MI	5 y	25(OH)D	<50 nmol/L	31	736	1.20	0.7, 2.2	0.52	A
					≥50 nmol/L	21	735	1.00	Reference		
		Primary–Stroke	5 y	25(OH)D	<50 nmol/L	37	736	1.40	0.8,2.5	0.20	
					≥50 nmol/L	22	735	1.00	Reference		
		Primary–MI, Stroke, or sudden death	5 y	25(OH)D	<50 nmol/L	65	736	1.20	0.8, 1.8	0.34	
					≥50 nmol/L	45	735	1.00	Reference		
		Primary–TIA	5 y	25(OH)D	<50 nmol/L	24	736	1.10	0.6, 2.0	0.76	
					≥50 nmol/L	21	735	1.00	Reference		
		Primary–Congestive heart failure	5 y	25(OH)D	<50 nmol/L	12	736	1.00	0.4, 2.4	0.97	
					≥50 nmol/L	10	735	1.00	Reference		
		Primary–Death	5 y	25(OH)D	<50 nmol/L	34	736	0.90	0.5, 1.6	0.73	
					≥50 nmol/L	29	735	1.00	1.00		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Brondum-Jacobsen 2012[69]	51–70 years	Primary–Nonfatal ischemic heart disease	29 y	25(OH)D	<25.0 nmol/L	381	2,553	1.08	0.85, 1.37	0.1	B
					25.0–49.9 nmol/L	648	4,068	1.01	0.81, 1.26		
					50.0–74.9 nmol/L	391	2,470	0.91	0.72, 1.15		
					≥75.0 nmol/L	158	1,079	1.00	Reference		
		Primary–Nonfatal MI	29 y	25(OH)D	<25.0 nmol/L	224	2,553	1.17	0.83, 1.63	0.4	
					25.0–49.9 nmol/L	350	4,068	0.97	0.71, 1.34		
					50.0–74.9 nmol/L	228	2,470	1.02	0.74, 1.42		
					≥75.0 nmol/L	89	1,079	1.00	Reference		
		Primary–Fatal ischemic heart disease/MI	29 y	25(OH)D	<25.0 nmol/L	422	2,553	1.53	1.18, 1.98	<0.001	
					25.0–49.9 nmol/L	627	4,068	1.23	0.96, 1.58		
					50.0–74.9 nmol/L	367	2,470	1.18	0.91, 1.54		
					≥75.0 nmol/L	106	1,079	1.00	Reference		
Brondum-Jacobsen 2013[92]	51–70 years	Primary–Ischemic stroke	29 y	25(OH)D	<25.0 nmol/L	350	2,553	1.36	1.09, 1.70	<0.001	A
					25.0–49.9 nmol/L	504	4,068	1.10	0.89, 1.36		
					50.0–74.9 nmol/L	277	2,470	0.92	0.74, 1.16		
					≥75.0 nmol/L	125	1,079	1.00	Reference		
deBoer 2012[87]		MI	11 y	25(OH)D	Normal level	154	1126	HR 1.00	Reference	NR	A
					Low level (season specific, ranges 43–61 nmol/L)	67	495	HR 1.24	0.91–1.70		
Deo 2011[78] Cardiovascular Health Study	≥ 65 years	Primary–Sudden cardiac death	14 y (median)	25(OH)D	<50 nmol/L	31	715	1.47	0.88, 2.46	Not sig	A
					≥50 nmol/L	42	1,568	1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Eaton 2011[70]	Post-meno-pausal women 50–79 years	Cardiovascular disease mortality	10 y	25(OH)D	Quartile 1: 3.25–36.50 nmol/L		608	HR 1.27	0.81, 1.99	0.33	A
					Quartile 2: 36.51–49.95 nmol/L		606	HR 1.14	0.74, 1.78		
					Quartile 3: 49.96–65.38 nmol/L		608	HR 1.16	0.75, 1.80		
					Quartile 4: 65.39–146.67 nmol/L		607	HR 1.00	Reference		
Fiscella 2010[71] NHANES-III		Primary–Cardiovascular death	138,549 person years	25(OH)D	Q1: <45 nmol/L	933	15363	1.00	Reference		A
					Q2: 45–62.25 nmol/L			0.71	0.54, 0.94	NR	
					Q3: 62.5–79.75 nmol/L			0.65	0.53, 0.79	NR	
					Q4: >80 nmol/L			0.79	0.62, 1.01	NR	
					<45 nmol/L	933	15363	1.40	1.16, 1.69	<0.001	
					≥45 nmol/L			1.00	Reference		
Ginde 2009[72]	>/= 65 years	Cardiovascular death	7.3 y	25(OH)D	<25.0 nmol/L	767	115	2.36	1.17, 4.75	<0.05	B
					25.0–49.9 nmol/L		904	1.54	1.01, 2.34	<0.05	
					50.0–74.9 nmol/L		1296	1.26	0.85, 1.88	NS	
					75.0–99.9 nmol/L		775	1.20	0.79, 1.81	NS	
					≥100.0 nmol/L		318	1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Hutchinson 2010[79]	25–84 yrs										B
non-smokers		CVD mortality	11.7 y	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)	106	1184	HR 1.08	0.79–1.48	NR	
					Quartile 2: mean=46.7 (sd=6.0)	81	1187	HR 0.84	0.61–1.15		
					Quartile 3: mean=56.2 (sd=6.0)	62	1192	HR 0.71	0.51–1.01		
					Quartile 4: mean=72.3 (sd=13.2)	76	1188	HR 1.00	Reference		
smokers		CVD mortality	11.7 y	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)	45	597	HR 0.93	0.61–1.44	NR	
					Quartile 2: mean=46.7 (sd=6.0)	57	606	HR 1.10	0.73–1.67		
					Quartile 3: mean=56.2 (sd=6.0)	46	607	HR 1.04	0.67–1.60		
					Quartile 4: mean=72.3 (sd=13.2)	40	600	HR 1.00	Reference		
Jassal 2010[80]		Primary–Cardiovascular mortality	10.4 y	25(OH)D	per SD increase in serum 25(OH)D	111	1073	1.07	0.86, 1.33	NS	A
					per SD increase in log of serum 1,25(OH)2D	111	1073	0.98	0.80, 1.21	NS	

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Karakas 2013[61] MONICA/KORA Augsburg case-cohort study	Men 35–74 years	Primary–Coronary heart disease	11 y	25(OH)D in men	54.14–153.92 nmol/L	225	964	0.84	0.52, 1.35	0.461	A
					35.05–54.13 nmol/L			0.66	0.43, 1.02		
					5.08–35.02 nmol/L			1.00	Reference		
	Women 35–74 years		11 y	25(OH)D in women	47.70–127.69 nmol/L	73	819	0.42	0.19, 0.93	0.028	
					33.16–47.69 nmol/L			0.67	0.35, 1.29		
					9.87–33.15 nmol/L			1.00	Reference		
Kestenbaum 2011[81] CHS	>65 years	Primary–Cardiovascular mortality	14 y	25(OH)D	Continuous per 25nmol/L lower 25(OH)D	389	2312	1.06	0.94, 1.19	0.356	B
					<37.5nmol/L	107	681	1.17	0.83, 1.67		
					37.5–75nmol/L	207	1247	1.01	0.78, 1.30		
					>75nmol/L	75	384	1.00	Reference		
		Primary–Incident heart failure	14 y	25(OH)D	Continuous per 25nmol/L lower 25(OH)D	504	2312	0.95	0.86, 1.05	0.303	
					<37.5nmol/L	107	681	1.17	0.83, 1.67		
					37.5–75nmol/L	207	1247	1.01	0.78, 1.30		
					>75nmol/L	75	384	1.00	Reference		
		Primary–Incident myocardial infarction	14 y	25(OH)D	Continuous per 25nmol/L lower 25(OH)D	299	2312	1.25	1.08, 1.44	0.002	
					<37.5nmol/L	88	681	1.40	0.93, 2.12		
					37.5–75nmol/L	161	1247	1.20	0.90, 1.59		
					>75nmol/L	50	384	1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Kilkkinen 2009[82]	≥ 30 years	Primary–Cardiovascular death	27.1 y (median)	25(OH)D	M:62–180 nmol/l |F:56.0–151.0 nmol/l	150	1253	0.76	0.61, 0.95	0.005	A
					M:48.0–61.0 nmol/l |F:44.0–55.0 nmol/l	171	1222	0.86	0.70, 1.06		
					M:38.0–47.0 nmol/l |F:34.0–43.0 nmol/l	164	1284	0.81	0.66, 1.00		
					M:29.0–37.0 nmol/l |F:26.0–33.0 nmol/l	194	1202	1.04	0.86, 1.26		
					M:5.0–28.0 nmol/l |F:4.0–25.0 nmol/l	254	1258	1.00	Reference		
		Primary–Cerebrovascular death	27.1 y (median)	25(OH)D	M:62–180 nmol/l |F:56.0–151.0 nmol/l	33	1253	0.48	0.31, 0.75	0.002	
					M:48.0–61.0 nmol/l |F:44.0–55.0 nmol/l	48	1222	0.69	0.48, 1.00		
					M:38.0–47.0 nmol/l |F:34.0–43.0 nmol/l	68	1284	0.97	0.70, 1.35		
					M:29.0–37.0 nmol/l |F:26.0–33.0 nmol/l	52	1202	0.80	0.57, 1.14		
					M:5.0–28.0 nmol/l |F:4.0–25.0 nmol/l	92	1258	1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
		Primary–Coronary disease death	27.1 y (median)	25(OH)D	M:62–180 nmol/l |F:56.0–151.0 nmol/l	117	1253	0.91	0.70, 1.18	0.2	
					M:48.0–61.0 nmol/l |F:44.0–55.0 nmol/l	123	1222	0.95	0.74, 1.22		
					M:38.0–47.0 nmol/l |F:34.0–43.0 nmol/l	96	1284	0.73	0.56, 0.95		
					M:29.0–37.0 nmol/l |F:26.0–33.0 nmol/l	142	1202	1.17	0.93, 1.48		
					M:5.0–28.0 nmol/l |F:4.0–25.0 nmol/l	162	1258	1.00	Reference		
Lin 2012[83]	Men 40–69 yrs	Cerebrovascular death	24 y	25(OH)D	continuous 25(OH)D	279	1101	HR 1.05	0.98, 1.12	0.141	B
						157	608	HR 1.04	0.96, 1.13	0.337	
	Women 40–69 yrs					122	493	HR 1.06	0.96, 1.17	0.277	
	Men 40–69 yrs	cardiovascular death	24 y	25(OH)D	continuous 25(OH)D	200	1101	HR 0.98	0.91, 1.06	0.678	
						119	608	HR 0.94	0.85, 1.04	0.223	
	Women 40–69 yrs					81	493	HR 1.06	0.93, 1.20	0.399	
Messenger 2012[59] MrOS	≥ 65 yrs	Primary–Cardiovascular disease(CHD & CVA)	4.4 y (median)	Dietary Vit D intake	<168.6 IU	107	3094	0.76	0.56, 1.04	0.29	A
					168.6–437.8 IU	125		0.97	0.72, 1.30		
					437.9–572.3 IU	108		0.85	0.63, 1.15		
					>572.3 IU	132		1.00	Reference		
			4.4 y (median)	25(OH)D	12–50.25 nmol/L	39	204	1.18	0.69, 2.03	0.85	
					50.5–63nmol/L	33	203	1.11	0.65, 1.91		
					63.25–75 nmol/L	35	202	0.97	0.57, 1.64		
					75.25–138.5 nmol/L	33	204	1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Michaelsson 2010[84]	birth 1920–1924	cardiovascular mortality	12.7 y	25(OH)D	< 10th percentile (<46 nmol/L)	24	119	HR 1.53	0.97, 2.41		B
					10th–90th percentile (46–93 nmol/L)	135	956	HR 1.00	Reference		
					>90th percentile (>93 nmol/L)	18	119	HR 1.16	0.69, 1.93		
Prentice 2013[2] WHI		Primary–MI	7.2 y	25(OH)D	≥400IU/day	40	1,914	1.06	0.75, 1.51	0.38	A
					no supplementation	433	23,561	1.00	Reference		
		Primary–Coronary heart disease			≥400IU/day	50	1,914	0.74	0.58, 0.95	0.53	
					no supplementation	545	23,561	1.00	Reference		
		Primary–Total heart disease			≥400IU/day	132	1,914	0.96	0.79, 1.16	0.82	
					no supplementation	1602	23,561	1.00	Reference		
		Primary–Stroke			≥400IU/day	38	1,914	0.84	0.66, 1.07	0.47	
					no supplementation	471	23,561	1.00	Reference		
		Primary–Total cardiovascular disease			≥400IU/day	181	1,914	0.92	0.778, 1.09	0.81	
					no supplementation	2187	23,561	1.00	Reference		
Schierbeck 2012[88] Danish Osteoporosis Prevention Study		Primary–Heart failure	16 y	25(OH)D	<50 nmol/l	10	788	1.88	0.71, 5.01	0.206	B
					≥50 nmol/l	8	1225	1.00	Reference		
		Primary–Myocardial Infarction			<50 nmol/l	13	788	0.83	0.41, 1.67	0.597	
					≥50 nmol/l	22	1225	1.00	Reference		
		Primary–Stroke			<50 nmol/l	47	788	1.68	1.10, 2.56	0.017	
					≥50 nmol/l	42	1225	1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Semba 2010[93]		all-cause mortality	6.5 yrs	25(OH)D	1st quartile: <26.25 nmol/L	NR	252	HR 2.11	1.22, 3.64		B
					2nd quartile: 26.25–40.0 nmol/L	NR	254	HR 1.41	0.83, 2.40		
					3rd quartile: 40.25–64 nmol/L	NR	247	HR 1.12	1.09, 1.15		
					4th quartile: >64 nmol/L	NR	253	HR 1.00	Reference		
		cardiovascular mortality			1st quartile: <26.25 nmol/L	NR	252	HR 2.23	0.95, 5.25		
					2nd quartile: 26.25–40.0 nmol/L	NR	254	HR 1.58	0.71, 3.53		
					3rd quartile: 40.25–64 nmol/L	NR	247	HR 2.11	1.01, 4.43		
					4th quartile: >64 nmol/L	NR	253	HR 1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Signorello 2010[74]					Quartile 4: (>54.1 nmol/L)	41	109	1.00	Reference	0.01	A
African Americans		circulatory disease death	NR	25(OH)D	Quartile 3: (37.9–54.1 nmol/L)	76	162	1.67	0.95, 2.93		
					Quartile 2: (25.45–37.88 nmol/L)	116	225	1.78	1.05, 3.01		
					Quartile 1: <25.45 nmol/L)	144	258	2.53	1.44, 4.46		
					Quartile 4: (>54.1 nmol/L)	40	107	1.00	Reference	0.01	
non-African Americans		circulatory disease death	NR	25(OH)D	Quartile 3: (37.9–54.1 nmol/L)	38	84	1.09	0.51. 2.30		
					Quartile 2: (25.45–37.87 nmol/L)	37	56	3.66	1.50, 8.95		
					Quartile 1: <25.45 nmol/L)	39	61	3.25	1.33, 7.93		
Sun 2012[90] Nurses' Health Study		Primary–Ischemic stroke	17 y	25(OH)D	9.2–45.7 nmol/l	171	325	1.49	1.01, 2.18	0.04	A
					45.8–65.4 nmol/l	160	314	1.26	0.89, 1.79		
					66.5–264.3 nmol/l	133	289	1.00	Reference		
Welsh 2012[60] MIDSPAN Family Study		Primary—Cardiovascular event	14.4 y (median)	Dietary Vit D intake	per 1 SD increase in dietary Vit D intake-log scale	293	1492	0.94	0.83, 1.08	NR	B
				25(OH)D	per 1 SD increase in 25(OH)D-log scale	293	1492	1.07	0.94, 1.23	NR	
				25(OH)D	<37.5 nmol/L	293	1492	1.00	0.77, 1.31	NR	
				25(OH)D	≥37.5 nmol/L			1.00	Reference		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Tomson 2013[75] Whitehall study		Death, ischemic heart disease	13.1 yrs	25(OH)D	Doubling Concentration	659	5409	0.84	0.70, 1.02		B
		Death, stroke				378	5409	0.81	0.63, 1.03		
		Death, other vascular				321	5409	0.71	0.54, 0.93		
		Death, all vascular				1358	5409	0.80	0.70, 0.91		
Robinson-Cohen 2013[62] MESA		incident coronary heart disease events	8.5 yrs	25(OH)D	<85.92	120	2131	1.32	0.95, 1.83	0.04	A
					85.92–124.58	134	2224	1.20	0.91, 1.58		
					>=124.58	107	2081	1.00	Reference		
					per 42.96 decrement	361	6436	1.15	1.01, 1.32		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Perna 2013[63]		total cvd	6.5 yrs	25(OH)D	< 30	171	1114	1.24	1.02, 1.50		
					30–<50	448	3430	1.14	0.99, 1.32		
					>=50	392	3165	1.00	Reference		
					per 25	1011	7709	0.95	0.89, 1.01		
		nonfatal cvd			< 30	136	1114	1.17	0.94, 1.45		
					30–<50	383	3430	1.15	0.98, 1.35		
					>=50	335	3165	1.00	Reference		
					per 25	854	7709	0.98	0.91, 1.05		
		fatal cvd			< 30	40	1114	1.55	1.01, 2.37		
					30–<50	71	3430	1.05	0.73, 1.49		
					>=50	65	3165	1.00	Reference		
					per 25	176	7709	0.89	0.66, 0.94		
		total chd			< 30	92	1114	1.32	1.02, 1.72		
					30–<50	236	3430	1.19	0.98, 1.45		
					>=50	208	3165	1.00	Reference		
					per 25	536	7709	0.92	0.84, 1.01		
		nonfatal chd			< 30	77	1114	1.28	0.97, 1.71		
					30–<50	204	3430	1.18	0.95, 1.46		
					>=50	179	3165	1.00	Reference		B
					per 25	460	7709	0.96	0.88, 1.06		
		fatal chd			< 30	16	1114	1.53	0.80, 2.94		
					30–<50	32	3430	1.18	0.70, 1.99		
					>=50	31	3165	1.00	Reference		
					per 25	79	7709	0.7	0.54, 0.93		
		total stroke			< 30	64	1114	1.31	0.95, 1.81		
					30–<50	165	3430	1.2	0.94, 1.54		
					>=50	124	3165	1.00	Reference		
					per 25	353	7709	0.91	0.81, 1.02		
		nonfatal stroke			< 30	55	1114	1.26	0.89, 1.77		
					30–<50	146	3430	1.19	0.92, 1.55		
					>=50	112	3165	1.00	Reference		
					per 25	313	7709	0.91	0.81, 1.02		
		fatal stroke			< 30	9	1114	1.86	0.74, 4.66		
					30–<50	20	3430	1.44	0.68, 3.03		
					>=50	12	3165	1.00	Reference		
					per 25	41	7709	0.86	0.61, 1.23		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Schottker 2013[76] ESTHER		CVD mortality	9.5 yrs	25(OH)D	<30	71	1439	1.29	0.94, 1.76		B
					30–50	137	4188	0.94	0.73, 1.21		
					>50	142	3927	1.00	Reference		
Skaaby 2013[86] Monica10 and Inter99		ischemic heart disease	10 yrs	25(OH)D	per 10nmol/L	478	8131	1.01	0.98, 1.05	0.44	B
					Q1			1.00	Reference	0.25	
					Q2			1.17	0.91, 1.51		
					Q3			1.00	0.76, 1.31		
					Q4			1.24	0.95, 1.62		
		stroke			per 10nmol/L	316	8131	1.00	0.96, 1.05	0.92	
					Q1			1.00	Reference	0.78	
					Q2			1.08	0.79, 1.49		
					Q3			1.18	0.86, 1.63		
					Q4			1.13	0.80, 1.59		
Kuhn 2013[65] EPIC-Germany		Myocardial Infarction	7.6 yrs	25(OH)D	Q4: median 66.5	118	533	1.00	Reference	0.19	A
					Q3: median 50.5	117	533	0.95	0.70, 1.28		
					Q2: median 40.4	158	533	1.24	0.93, 1.66		
					Q1: median 28.9	166	533	1.43	1.07, 1.92		
		stroke			Q4: median 66.6	111	533	1.00	Reference	0.19	
					Q3: median 50.5	101	533	0.86	0.63, 1.17		
					Q2: median 40.4	102	533	0.83	0.61, 1.12		
					Q1: median 28.9	157	533	1.37	1.02, 1.84		
		CVD as composite endpoint			Q4: median 66.5	229	533	1.00	Reference	0.12	
					Q3: median 50.5	218	533	0.89	0.70, 1.14		
					Q2: median 40.4	260	533	1.06	0.83, 1.35		
					Q1: median 28.9	323	533	1.41	1.11, 1.79		

Table 11a. Vitamin D and cardiovascular outcomes: Results of cohort studies (updated from original report) (continued)

Author Year Study Name (PMID)	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Brodin 2013[91] Tromso study		total venous thromboembolism	10.7 yrs	25(OH)D	<=44	50	1474	1.00	Reference	0.89	A
					45–56	58	1470	0.72	0.41, 1.30		
					57–69	46	1481	0.93	0.55, 1.50		
					>=70	47	1480	0.76	0.45, 1.28		
					per 1 sd decrease in serum 25ohd	201	5905	1.02	0.91, 1.22		
Formiga 2014[77] Octabaix		Cardiovascular mortality	2.8 yrs	25(OH)D	Q1: <34.94	6	71	1.04	0.33, 3.24	0.86	B
					Q2: 34.94–61.65	6	77	0.89	0.28, 2.80		
					Q3: 61.66–83.37	6	84	1.47	0.45, 4.58		
					Q4:>83.37	7	80	1.00	Reference		

*Statistically significant (P<0.05)

Table 11b. Vitamin D and cardiovascular outcomes: Results of nested case-control studies (new table)

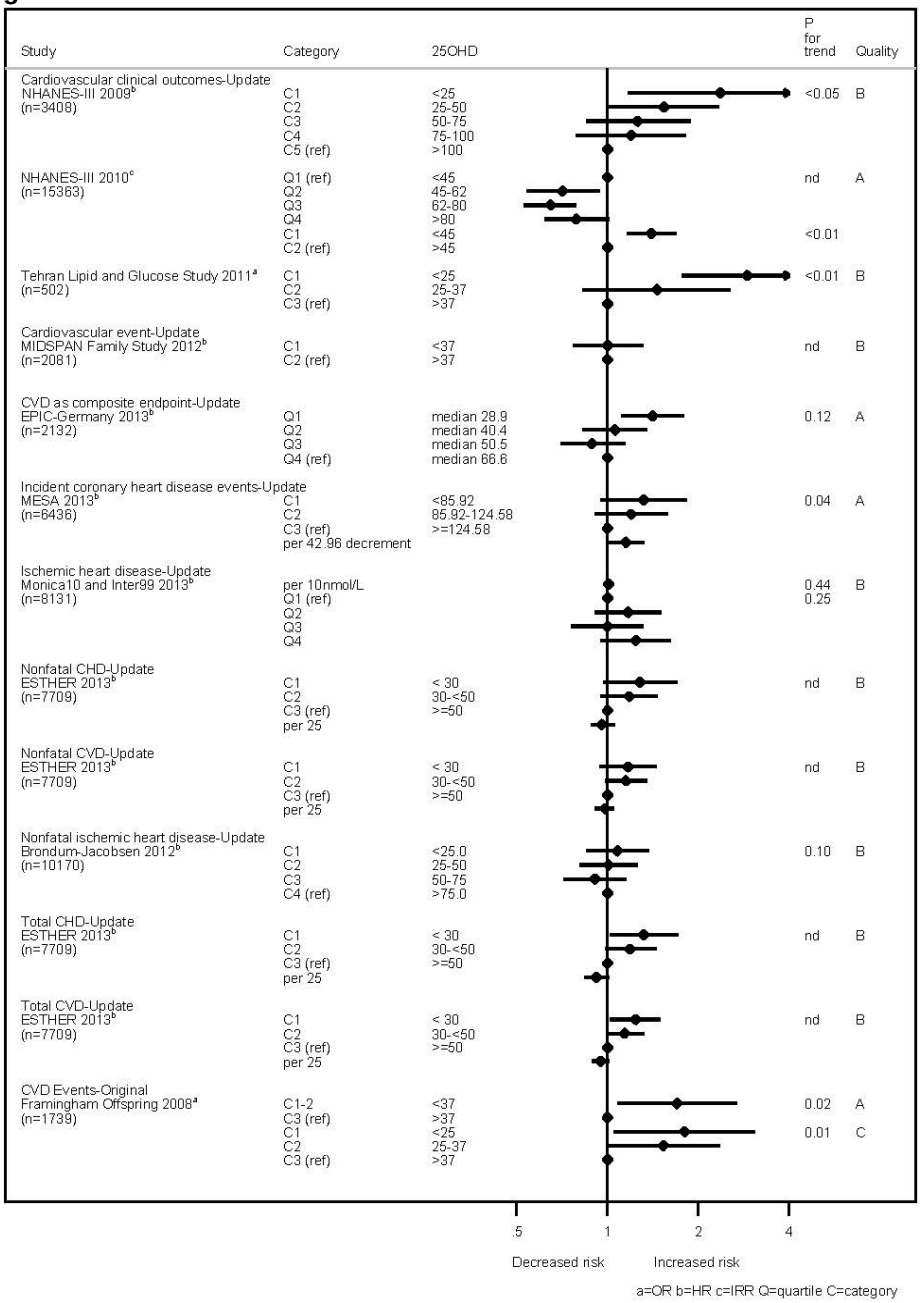
Author Year Study Name [PMID]	Age Range, Sex	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Hosseinpanah 2011[64] Tehran Lipid and Glucose Study (TLGS)	19–70 years	Primary–Cardiovascular disease	5.7 y	25(OH)D	<25.0 nmol/L	85	133	2.90	1.76, 4.67	<0.001	B
					25–37.48 nmol/L	86	173	1.46	0.83, 2.56	0.18	
					≥37.5 nmol/L	80	196	1.00	**Reference**		
Pilz 2009[73]		cardiovascular mortality	6.2 y	25(OH)D	1st quartile (mean 25(OH)D 30.6 nmol/L)	12	152	5.38	2.02, 14.34	0.001	B
					2nd–4th quartiles (mean 25(OH)D 45.6–78.9)	8	462	1.00	**Reference**		

[A]Multivariable Cox regression with continuous 25(OH)D and regression splines with nonlinear relationships suggests an increased hazard of CVD events at serum 25(OH)D concentrations below approximately 50–55 nmol/L. See Figure 2 on page 508 of article.

[B]Adjusted regression analyses found OR=0.98 (0.96, 0.998) per 2.5 nmol/L increase in 25(OH)D and risk reduction of -2.1% (-0.2%, -4.0%) per 2.5 nmol/L increase in serum 25(OH)D concentration.

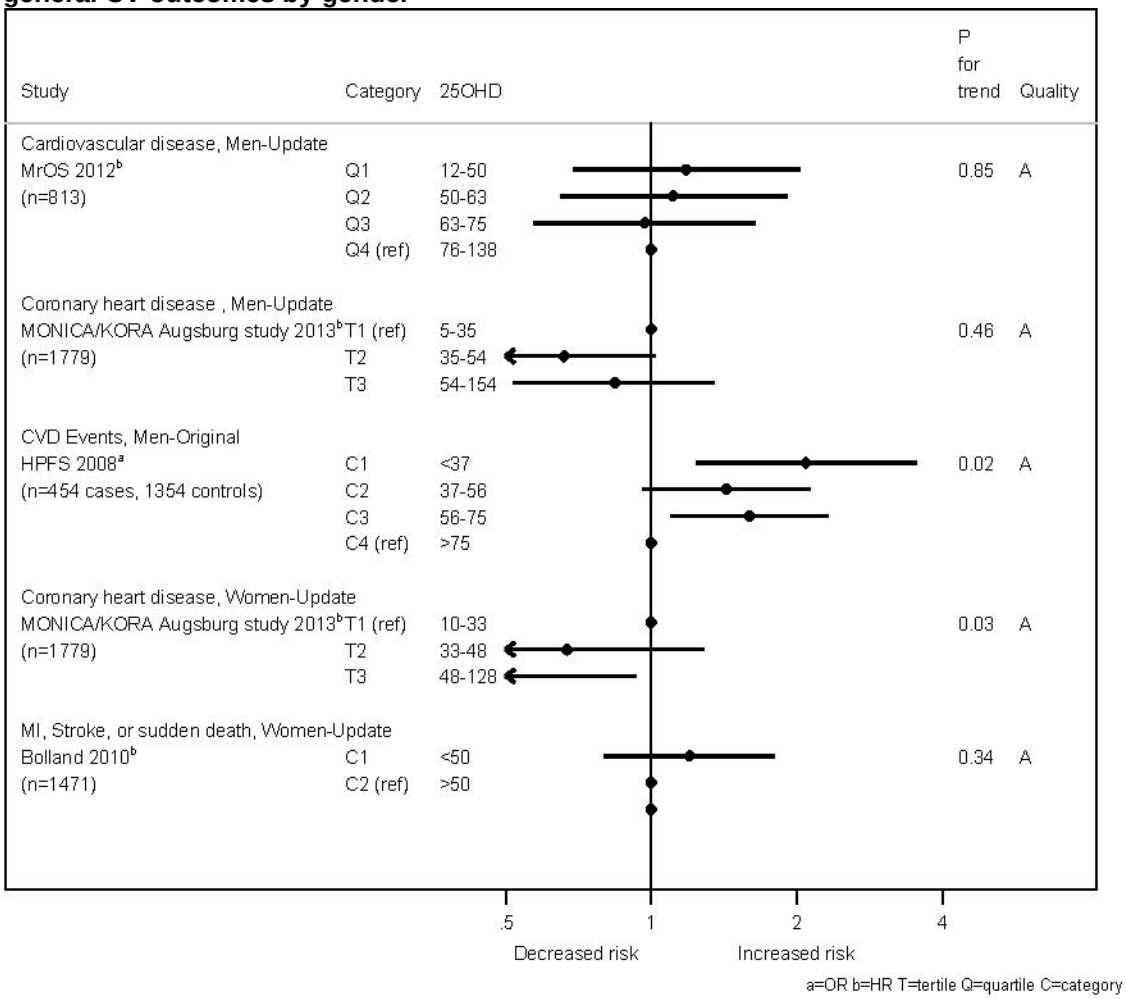
[C]In a subgroup analysis of participants on no cholesterol lowering drugs at baseline, comparing the highest serum 25(OH)D concentration category (>75 nmol/L) to the lowest (≤37.5 nmol/L), adjusted RR=2.30 (1.33, 3.97).

Figure 6a. Cardiovascular outcomes risk stratified by vitamin D concentration for combined and general CV outcomes



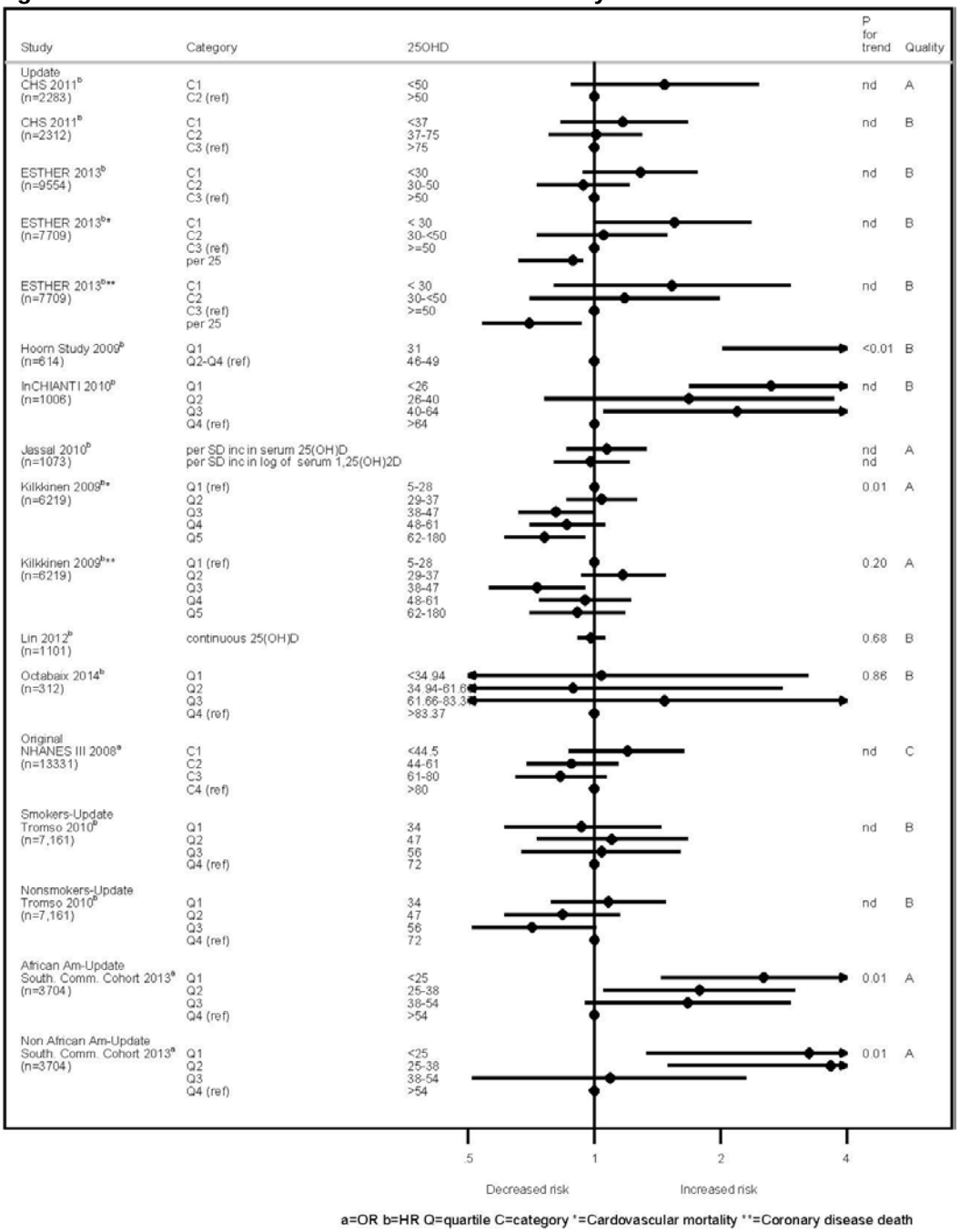
Abbreviations: CVD = cardiovascular disease; EPIC = European Prospective Investigation into Cancer; ESTHER = EStrogen and THromboEmbolism Risk Study; MESA = Multi-ethnic Study of Atherosclerosis; NHANES = National Health and Nutrition Examination Study

Figure 6b. Cardiovascular outcomes risk stratified by vitamin D concentration for combined and general CV outcomes by gender



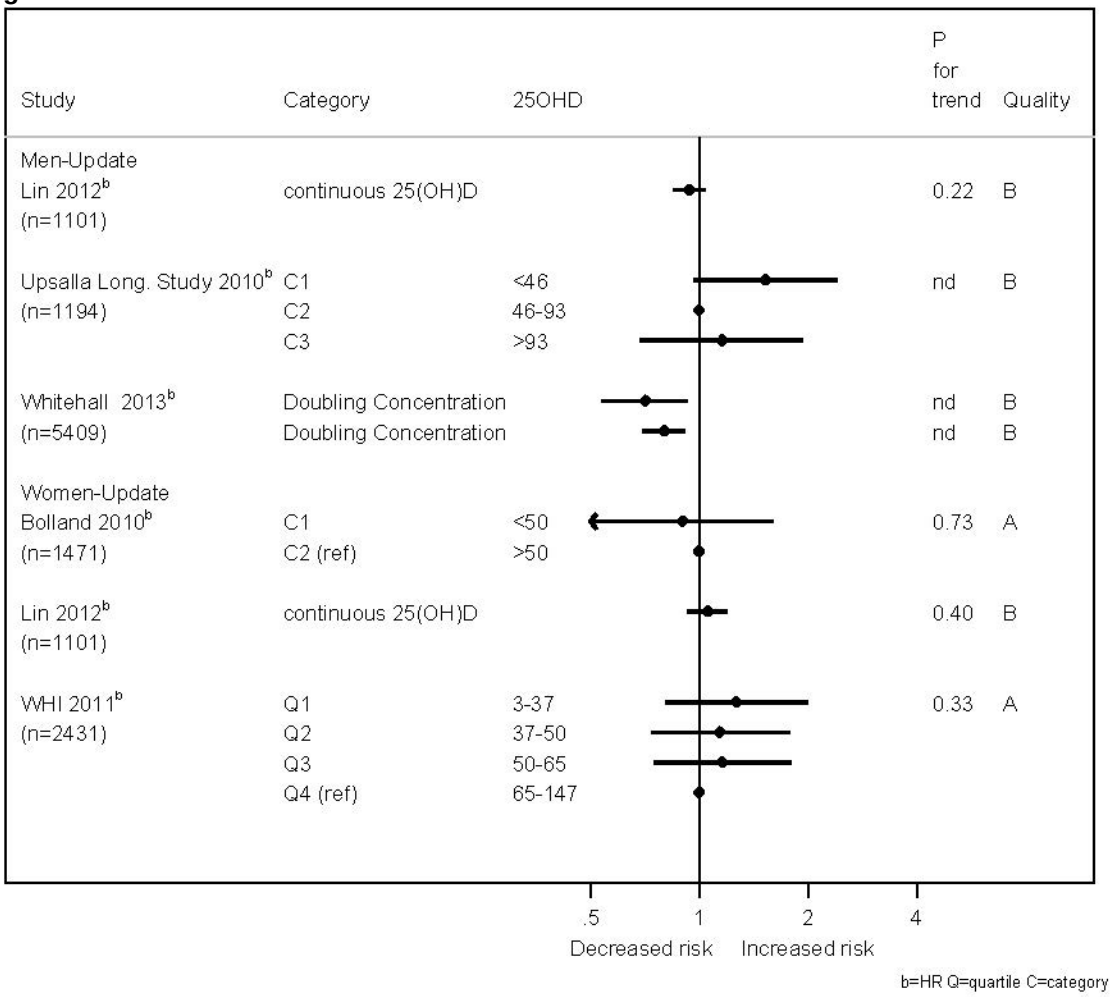
Abbreviations: MONICA = Multinational MONItoring of trends and determinants in CArdiovascular disease Study; KORA = Cooperative Health Research in the Region Augsburg; HPFS = Health Professionals Follow-Up Study

Figure 6c. Cardiovascular outcomes risk stratified by vitamin D concentration for CV mortality



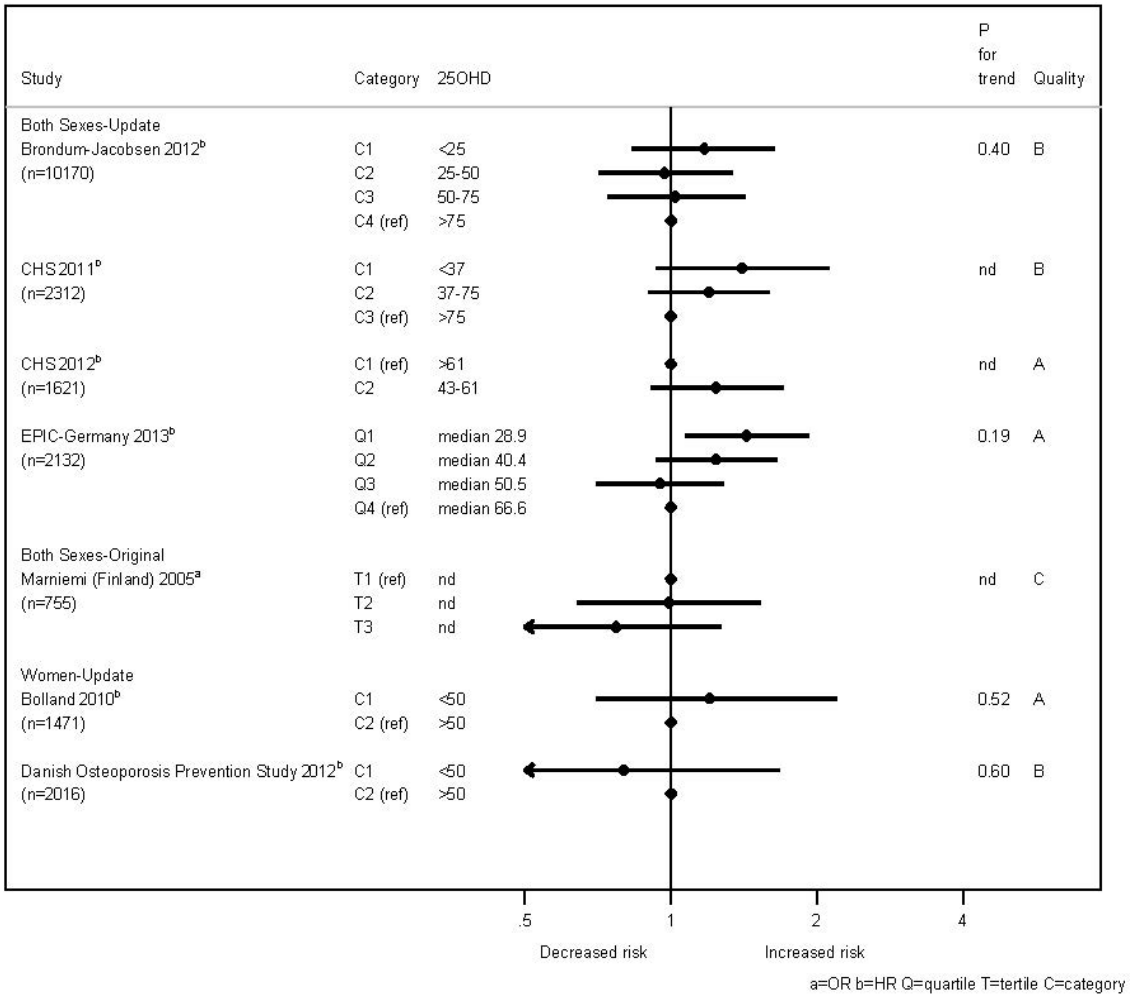
Abbreviations: InChianti = Invecchiare nel Chianti; CHS = Cardiovascular Health Study; NHANES = National Health and Nutrition Examination Study; ESTHER = EStrogen and THromboEmbolism Risk Study

Figure 6d. Cardiovascular outcomes risk stratified by vitamin D concentration for CV mortality by gender



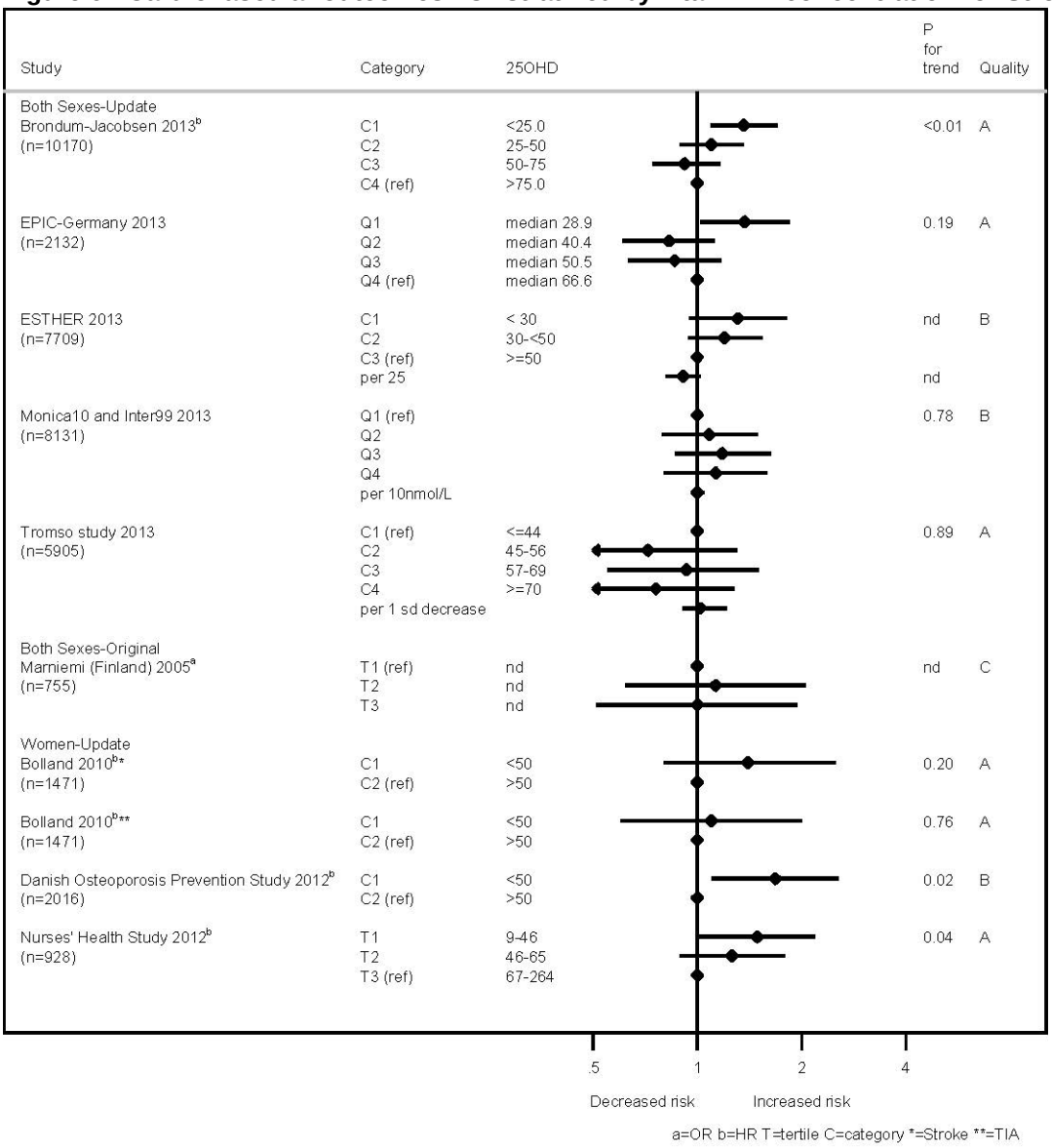
Abbreviation: WHI = Women's Health Initiative

Figure 6e. Cardiovascular outcomes risk stratified by vitamin D concentration for myocardial infarction



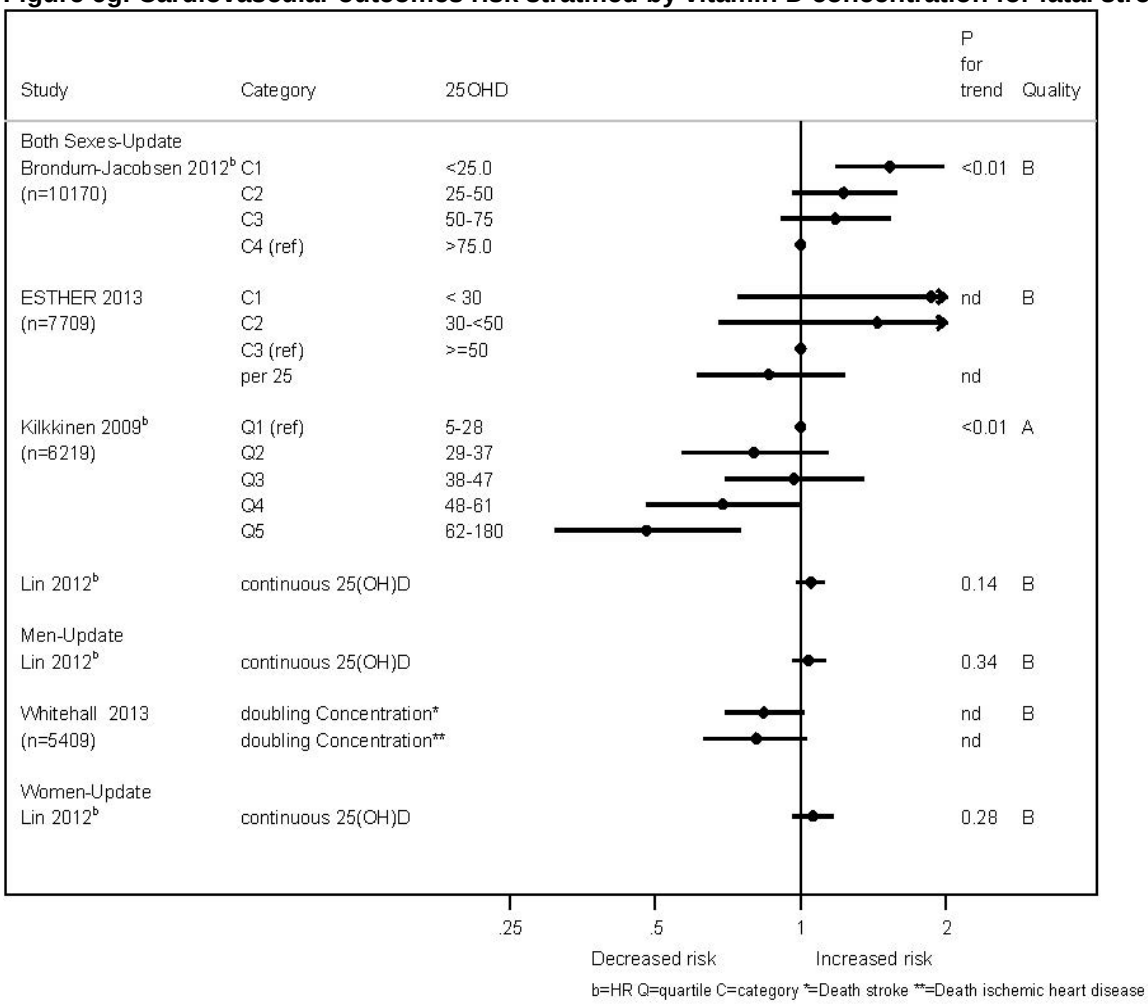
Abbreviations: CHS = Cardiovascular Health Study; EPIC = European Prospective Investigation into Cancer

Figure 6f. Cardiovascular outcomes risk stratified by vitamin D concentration for Stroke/TIA]



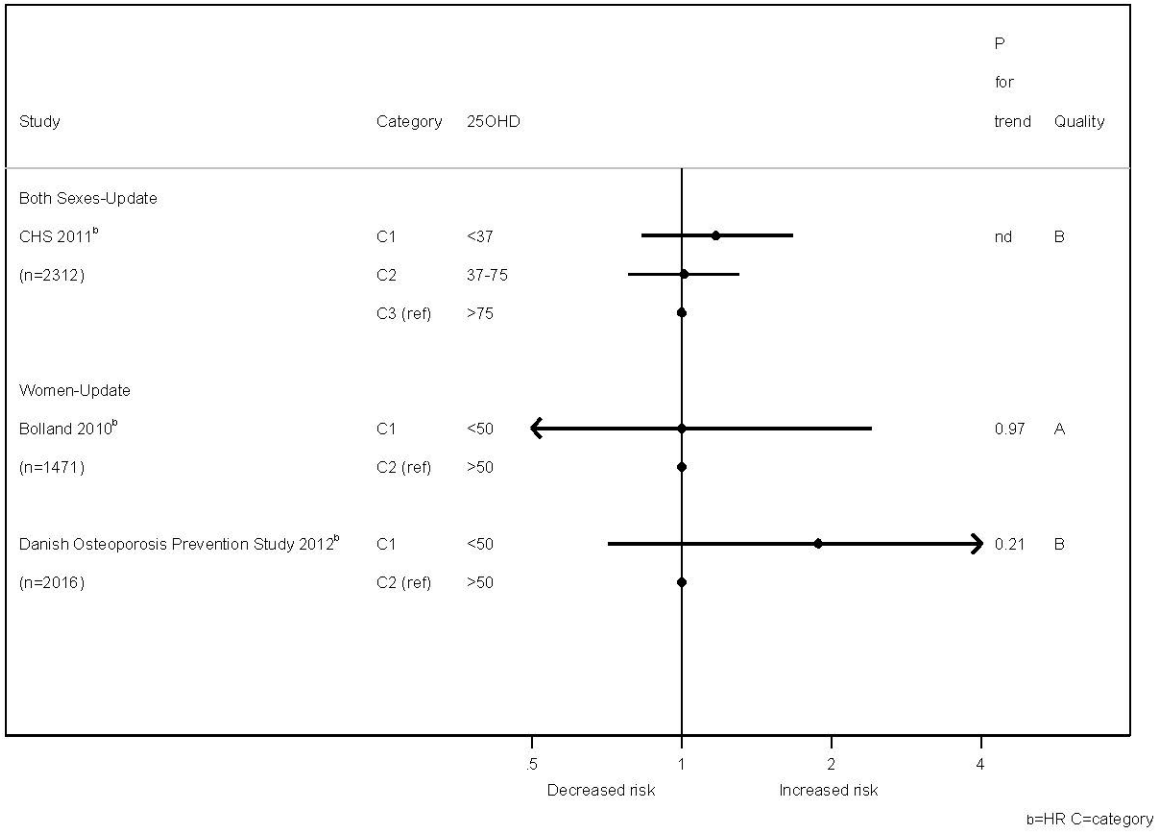
Abbreviations: EPIC = European Prospective Investigation into Cancer; ESTHER = EStrogen and THromboEmbolism Risk Study

Figure 6g. Cardiovascular outcomes risk stratified by vitamin D concentration for fatal stroke



Abbreviation: ESTHER = EStrogen and THromboEmbolism Risk Study

Figure 6h. Cardiovascular outcomes risk stratified by vitamin D concentration for congestive heart failure



Abbreviation: CHS= Cardiovascular Health study

Vitamin D and Body Weight

The current report did not assess the association between serum 25(OH)D concentrations and body weight. The original report searched for systematic reviews and primary studies that evaluated associations between vitamin D intake or body stores and *incidence of overweight or obesity*; no such studies were found. For the outcome *weight change* (in kilograms or body mass index units), only randomized controlled trials were included. The EPC and the TEP agreed that the limited resources would not be expended on reviewing observational studies for the surrogate outcome body weight (where overweight or obesity is considered to be the clinical outcomes). Only studies of adults were included. Studies of weight gain in children are included in the "Growth" section.

Synopsis

No qualified systematic reviews have evaluated the association between vitamin D intake or serum 25(OH)D concentrations and body weight in adults. Three RCTs from Finland, Norway, and India compared different doses of vitamin D (300 IU daily, 20,000 or 40,000 IU weekly, or 120,000 IU every 2 weeks) to placebo, with or without supplemental calcium in both groups. The study participants also varied: they were postmenopausal women, obese men and women, or only obese men. In the Finnish and Norwegian studies, the participants on average, gained weight in all groups over 1 or 3 years; in the Indian study weight remained mostly stable over 6 weeks. All studies found no difference in weight change with or without vitamin D supplementation.

Detailed Presentation (Tables 12 and 13)

Three RCTs of vitamin D reported body weight (or body mass index [BMI]) as an outcome. The Kuopio (Finland) Osteoporosis Risk Factor and Prevention Study (Kuopio ORFPS) included postmenopausal women in a four-arm study.[94] Two of the study arms included hormone replacement treatment and are not further discussed here. The remaining two arms compared vitamin D_3 300 IU (83 women) versus placebo (95 women), where all women were taking low dose calcium lactate 500 mg/d (equivalent to 93 mg Ca^{++}/d). Women on cholesterol-lowering medication at any point during the trial were excluded. The primary outcome of the trial was the serum lipid profile. The women ranged in age from 47 to 56 years. After 3 years, women, on average, gained weight in both study arms (about 1–2 kg). Those in the placebo arm gained an absolute 1.5 percent more weight than those in the vitamin D arm, but the difference was not statistically significant. The study had a methodological quality of C due to an uneven distribution of body weights between study arms at baseline (means 71.5 and 67.6 kg) and an overall withdrawal rate of over 30 percent.

The second trial was conducted in Norway among healthy overweight and obese women and men.[95] The participants' mean baseline serum 25(OH)D concentration was 53 nmol/L. The trial compared vitamin D_2 40,000 IU weekly (116 participants completed), 20,000 IU weekly (106 participants), and placebo (112 participants). All study participants also took calcium carbonate 500 mg daily. Almost all participants complied with the vitamin D (or placebo). Changes in weight and BMI were primary outcomes. The participants ranged in age from 21 to 70 years. After 1 year, changes in weight were small (increases of 0.1–0.5 kg) in each trial group. Compared to the placebo group, those taking the larger dose of vitamin D had less weight gain than those taking the smaller dose, but none of the differences among study groups were

statistically significant. The study was rated methodological quality B, primarily due to the high dropout rate (25 percent), which was not explained.

The third trial was conducted in New Delhi, India among healthy obese men.[96] The participants' mean baseline serum 25(OH)D concentration was about 33 nmol/L. The trial compared vitamin D_3 120,000 given under supervised conditions every 2 weeks and placebo in 100 men, of whom 71 were analyzed; most dropouts occurred because of refusals for subsequent blood draws (to assess the primary outcome). After 6 weeks, weight in kg and BMI were essentially stable, with no difference in weight change between the interventions. The study was rated methodological quality B because of the high dropout rate; for weight (in kg), the study was of quality C because baseline weights were not reported.

Findings per Vitamin D Dose

There was a lack of effect found across a range of doses from 300 IU to 8570 IU (prorated) daily.

Findings per Age and Sex

There was a lack of effect found in studies both of men mostly in their 40s, somewhat older people of both sexes, and postmenopausal women.

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  Not reviewed
- **19–50 y**
  No effect was found in one trial of men mostly within this life stage after 6 weeks.
- **51–70 y**
  The majority of people in the trials were within this life stage. No significant effect was found on weight from vitamin D supplementation for 1 or 3 years.
- **≥71 y**
  No data
- **Postmenopause**
  All the women in the Finnish trial were postmenopausal.
- **Pregnant & lactating women**
  Not reviewed

Table 12. Vitamin D and weight: Characteristics of RCTs [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Heikkinen 1997[94] Kuopio ORFPS Kuopio, Finland (63°N) [9405029]	• Health status • Mean age (range), y • Male (%)	All, post-menopause 53 (47-56) 0	nd	Vit D_3 & Ca lactate vs. Placebo & Ca lactate	nd	
Sneve 2008[95] Tromsø, Norway (70°N) [19056900]	• Health status • Mean age (range), y • Male (%)	Healthy overweight and obese 48 (21–70) 36	25(OH)D 53.1±16.9 nmol/L Ca intake 940±398 mg/d	Vit D_3 40,000 IU per week vs. Vit D_3 20,000 IU per week vs. Placebo All: Ca carbonate 500 mg/d	The compliance rate for cholecalciferol/placebo capsules were 95% in all 3 groups, and for the calcium tablets 81–85% across all 3 groups.	
Nagpal 2009[96] New Delhi, India (28.5°N) [19125756]	• Health status • Mean age (SD), y • Male (%)	Healthy, obese 44 (8) 100%	25(OH)D: 36.5 nmol/L (treatment group), 30.0 nmol/L (control group)	Vit D_3 120,000 IU every 2 weeks vs. Placebo	100% (implied); supervised home visits	Excluded subjects who refused subsequent blood draws

Table 13. Vitamin D and weight: Results of RCTs [no new studies in the current report]

Author Year Study Name [PMID]	Age Range, Sex (Subgroup)	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Isocaloric Diet														
Heikkinen 1997[94] Kuopio ORFPS [9405029]	47–56 y, Women	Weight	2°	3 y	Vit D_3 300 IU + Ca lactate 93 mg	83	kg	71.5	+1.84%	+0.43%, +3.25%	-1.5%	-3.6%, +0.6%[A]	NS[B]	C
					Ca lactate 93 mg	95		67.6	+3.32%	+1.73%, 4.91%				
Sneve 2008[95] [19056900]	21–70 y, Both	Weight	1°	1 y	Vit D_3 40,000 IU weekly + Ca carbonate 500 mg	116	kg	101.0	+0.1	-0.6, +0.8	-0.4	-1.3, +0.5[A]	NS	B
					Vit D_3 20,000 IU weekly + Ca carbonate 500 mg	106		98.6	+0.3	-0.3, +0.9	-0.2	-1.1, +0.7[A]	NS	
					Ca carbonate 500 mg	112		100.6	+0.5	-0.2, +1.2				
		BMI	1°	1 y	Vit D_3 40,000 IU weekly + Ca carbonate 500 mg	116	BMI	35.0	0.0	-0.2, +0.2	-0.2	-0.6, +0.2[A]	NS	
					Vit D_3 20,000 IU weekly + Ca carbonate 500 mg	106		34.4	+0.1	-0.1, +0.3	-0.1	-0.4, +0.2[A]	NS	
					Ca carbonate 500 mg	112		35.1	+0.2	-0.1, +0.5				
Nagpal 2009[96] New Delhi, India [19125756]	44 (8, SD) Men	Weight	2°	6 wk	Vit D_3 120,000 IU every 2 wk	35	kg	nd	+0.03	-0.6, +0.6	+0.42	-0.4, +1.2	NS	C
					Placebo	36		nd	-0.38	-0.9, +0.2				
		BMI	2°	6 wk	Vit D_3 120,000 IU every 2 wk	35	BMI	26.7	-0.02	-0.2, +0.2	+0.02	-0.3, +0.3	NS	B
					Placebo	36		26.0	-0.04	-0.3, +0.2				

[A]Estimated from reported data
[B]Per estimated 95% confidence interval, P=0.17
Note: Outcomes cells are shaded for the Control rows.

Vitamin D and Cancer

This section explores cancer from all causes and total cancer mortality.

Synopsis

No qualified systematic reviews have evaluated relationships between vitamin D and total cancer incidence or mortality. **No new RCTs were identified for the current report that addressed the effect of vitamin D or vitamin D combined with calcium on the risk for total cancer or cancer mortality. One cohort study found no association between total (all-cause) cancer and 25(OH)D concentrations (rated A), whereas a second cohort study observed an association in men but not in women (rated B). Ten cohort studies and one nested case control study addressed the association of serum 25(OH)D concentrations and cancer mortality. Five of the cohort studies (1 rated A, 4 rated B) observed no association of serum 25(OH)D concentration with total cancer mortality. Three cohort studies and the nested case control study observed a trend toward increased risk with decreased serum 25(OH)D (all rated B). One analysis using updated NHANES III data (rated B) observed a trend toward increasing risk for death with increasing serum 25(OH)D among men at higher latitudes whose blood was drawn in summer but the reverse in women. One cohort study observed a U-shaped association of increasing mortality with both low and high serum 25(OH)D.**

One RCT **in the original report** showed no effect of combined vitamin D_3 (1000 IU/d) and calcium (~1500 mg/d) supplementation versus calcium supplementation (~1500 mg/d) alone on the risk of total cancer in healthy postmenopausal women (>55 years old) living in Nebraska (latitude 41°N). Another RCT also found no difference in total cancer mortality or incidence between supplemental vitamin D_3 (100,000 IU every 4 months) and placebo in elderly (71+ years old) men and women living in the United Kingdom (latitude 52° N). Both RCTs were rated B quality.

Analyses using NHANES III data (general adult populations living in the United States) showed no significant association between baseline 25(OH)D concentrations and total cancer mortality.

Detailed Presentation (Tables 14, 15, 16, & 17)

Two cohort studies were identified for the current report that assessed the association between serum 25(OH)D and all-cause cancer. The Cardiovascular Health Study, conducted in four U.S. cities, tracked white adults 65 and over for a median of 11 years and found no association of cancer with seasonally adjusted serum 25(OH)D concentrations (rated A).[87] The ESTHER Study, conducted in Germany, tracked 9,580 men and women ages 50 to 74 for more than 8 years: this study found an association between decreased serum 25(OH)D and increased risk for any cancer in men but not in women (rated B).[97]

Eight observational studies were identified for the current report that assessed the association of serum 25(OH)D with cancer mortality.

The MrOS study, which followed men 65 and over in six U.S. cities for a 7.3-year followup, found an association of cancer mortality with serum 25(OH)D concentrations within the range clinically defined as vitamin D deficient but not with the lowest quartile of serum 25(OH)D (rated B).[98]

The Whitehall Study, a British study of 5,409 men with a followup of 13 years, observed a trend toward increasing risk for total cancer mortality with decreasing serum 25(OH)D (rated B).[75]

A substudy in 2,429 postmenopausal women within the Women's Health Initiative with measured baseline 25(OH)D concentrations were followed for 10 years. No association was seen between cancer mortality and serum 25(OH)D concentrations (rated A).[70]

The ESTHER Study observed a significant association between serum 25(OH)D in the lowest quartile and increased risk for total cancer mortality (rated B).[76]

The Copenhagen City Heart Study, which followed 9,791 adults for 28 years, observed no association between serum 25(OH)D and total cancer mortality (rated B).[99]

The General Population Trial of Linxian followed 29,584 men and women (40–69 years of age), of whom 217 died of cancer. No association was seen between serum 25(OH)D and risk for cancer death (rated B).[83]

The Southern Community Cohort Study, which followed some 85,000 men and women, ages 40 to 79 (about two-thirds of whom were African American), also observed no significant association between serum 25(OH)D concentrations and cancer death. No differences were seen between African Americans and whites or between men and women (rated A)[74]

An assessment of NHANES III data that stratified men and women by latitude and season of blood draw and followed them for an average of 13.4 years found a trend toward increased risk for cancer death with increasing serum 25(OH)D among men in higher latitudes with summer blood sampling but a decreased risk among women in this category; cancer deaths were not independently verified in this study(B).[100]

The Uppsala Longitudinal Study of Adult Men followed a population of elderly men (average age 71 years) for an average 12.7 years. This study observed a U-shaped association: both lower and higher serum 25(OH)D were associated with higher cancer mortality (<10th percentile: adjusted HR 1.99 [1.29, 3.08]; >90th percentile: adjusted HR 1.56 [0.95, 2.56]) (rated B).[84]

The Tromsø Study followed 7,161 men (age 55 to 74) and women (age 50 to 74), of whom 498 died of cancer over 11.7 years. A non-significant trend was observed between decreasing serum 25(OH)D and increasing cancer mortality (rated B).[79]

A nested case-control study conducted within the EPIC study that matched 541 individuals who died of colorectal cancer (CRC) with 661 controls (half were men; average age at diagnosis was 62) observed a small but significant trend toward increasing risk for CRC death and lower serum 25(OH)D however it was noted that a high proportion of the women in the cohort were taking bisphosphonates to prevent osteoporosis, which could have affected risk for cancer and mortality (rated B).[101]

From the original report, a 4-year population-based RCT,[102] sampled from a 9 county, largely rural area in eastern Nebraska (latitude 41°N), aimed to determine the efficacy of vitamin D_3 (1000 IU/d) plus calcium (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d) or calcium alone (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d) compared to placebo in reducing fracture incident. Only the comparison between the combined vitamin D and calcium versus the calcium alone groups is discussed here. The other comparisons are described in the calcium and combined vitamin D and calcium sections. This study was rated methodological quality B. Incidence of cancer was a secondary outcome of this trial. A total of 1179 postmenopausal women, aged more than 55 years old, were randomized. The mean

25(OH)D concentration at baseline was 72 nmol/L. The relative risk of developing cancer at the end of study was 0.76 (95% CI: 0.38, 1.55). On the hypothesis that cancers diagnosed early in the study would have been present, although unrecognized on entry, the analyses were restricted to women who were free of cancer at 1 year intervention. The relative risk of developing cancer at the end of study for the vitamin D_3 plus calcium group changed to 0.55 (95% CI 0.24, 1.28).

Another 5-year RCT compared the effects of supplemental vitamin D_3 (100,000 IU every 4 months) with placebo on total cancer mortality and incidence in 2686 elderly participants with a mean age of 75 years in the United Kingdom (latitude 52° N).[66] Total cancer mortality and incidence were evaluated as two of multiple secondary endpoints. The primary endpoint was the prevention of fracture. At 5 years vitamin D_3 supplementation had no significant effect on the prevention of total cancer mortality (HR 0.86; 95% CI 0.61, 1.20) or incidence (HR 1.09; 95% CI 0.86, 1.36). This trial was rated B because it did not report in sufficient detail the randomization method, and the outcome ascertainment was based on death certificates or self-reported data, not verified with another objective documents (e.g., medical records or pathology reports).

Reported in two publications (one was rated B and one was rated C), there was no association between baseline 25(OH)D concentrations and total cancer mortality in the total NHANES III study population[85,103] or in subgroup analyses by either season or latitude after a median 9 years of follow up.[103]

Findings by Age, Sex and/or Ethnicity

Of the studies identified for the current report, only one assessed differences in the association of serum 25(OH)D with total cancer mortality by ethnicity and saw no differences.[74] The analysis of NHANES III data observed apparently opposite associations between serum 25(OH)D concentrations between men and women of northern latitudes, as described above.[100]

Among studies identified for the original report, there were no differences in the total cancer mortality and incidence between men and women, reported in a 5-year RCT compared the effects of supplemental vitamin D_3 (100,000 IU every 4 months) with placebo. In the NHANES III analysis, there was a suggestion of increased risk of total cancer mortality in men whose baseline 25(OH)D were in the two highest categories (80 to <100 nmol/L; ≥100 nmol/L) compared to the reference category (<50 nmol/L) [80 to <100 nmol/L: RR = 1.21, 95% CI 0.83 to 1.78; ≥100 nmol/L: RR = 1.35; 95% CI 0.78 to 2.31; P for trend=0.08]. However, this relationship was not seen in women (P for trend=0.12).[103] When racial/ethnic groups were considered separately, there was also no association between baseline 25(OH)D concentrations and total cancer mortality in non-Hispanic whites (P for trend=0.80), non-Hispanic blacks (P for trend=0.14), or Mexican Americans (P for trend=0.37).

Findings by Life Stage

- **0–6 mo**
  No data
- **7 mo–2 y**
  No data
- **3–8 y**
  No data

- **9–18 y**
  No data
- **19–50 y**
  No studies identified for the current report assessed the association between serum 25(OH)D and total cancer mortality by age. Analyses using NHANES III data showed no significant association between baseline 25(OH)D concentrations and total cancer mortality. NHANES III included participants mostly within this life stage.
- **51–70 y**
  A proportion of participants in NHANES III were in this life stage, but no unique conclusions are possible for this life stage separate from those for people 19 to 50 years.
- **≥71 y**
  One RCT included elderly men and women mostly in this life stage. The trial found no difference in total cancer mortality or incidence between supplemental vitamin D_3 (100,000 IU every 4 months) and placebo.
- **Postmenopause**
  One assessment of postmenopausal women identified for the current study observed no association of serum 25(OH)D concentrations with total cancer death. One RCT with healthy postmenopausal women showed no effect of vitamin D_3 supplementation (1000 IU/d) on the risk of total cancer.
- **Pregnant & lactating women**
  No Data

Table 14. Vitamin D and total cancer and total cancer mortality: Characteristics of RCTs [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Lappe 2007[102] Nebraska, US (41º N) [17556697]	• Health status • Mean age (SD), y • Male (%)	Mentally and physically fit; post-menopause 67 (7.3) 0	25(OH)D: 71.8 nmol/L	Vit D_3 1000 IU/d + Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. placebo	nd	
Trivedi 2003[66] Oxford, UK (52°N) [12609940]	• Health status • Mean age (range), y • Male (%)	General population 75 (65–85) 76%	25(OH)D: 53.4 nmol/L Calcium intake= 742 mg/d (at 4 years, no difference by treatment allocation)	Vit D_3 100,000 IU vs. placebo every 4 months	Participants taking ≥80% of study medication: 76%[A]	Previous CVD: 28%, previous cancer: 6%, steroids user: 5%, and HRT taker: 7%

[A]No difference between the vitamin D and the placebo arm.

Table 15. Vitamin D and total cancer and total cancer mortality: Characteristics of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Cohort												
Freedman 2007[103] NHANES III US (various) [16481636]	• Health status • Mean age (range), y • Male (%)	Any 44 (≥17) 45	• Assay method • Season blood drawn	RIA (DiaSorin) All	Cancer mortality stratified by prespecified baseline 25(OH)D cut points	X	X	X	X	X	X	Final model includes sex, race/ethnicity, and smoking pattern. Other potential confounders were examined but not chosen.
Melamed 2008[85] NHANES III US (various) [18695076]	• Health status • Mean age (range), y • Male (%)	DM 7.4%, history of CVD 7.9%, HTN 25% 45 (≥20) 46	• Assay method • Season blood drawn	RIA (DiaSorin) All	Cancer mortality stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	
New Studies:												
Cawthon, 2010[98] MrOS	• Health status • Mean age (range), y • Male (%)	>80% excellent/good health status 74 (≥65) 100%			Cancer mortality stratified by baseline 25(OH)D quartiles and tertiles	X	X	X	X	X	X	MrOS study
de Boer, 2012[87] US (various)	• Health status • Mean age (SD), y • Male (%)	nd 74 (SD 4.6) 30%			Cancer stratified by baseline 25(OH)D median		X	X	X		X	
Eaton, 2011[70] US (various)	• Health status • Mean age (SD), y • Male (%)	nd 65.1 (7.6) 0%			Cancer mortality stratified by baseline 25(OH)D quartiles			X	X	X	X	

Table 15. Vitamin D and total cancer and total cancer mortality: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Freedman, 2010[100] US (various)	• Health status nd • Mean age (SD), y 44.5 • Male (%) 87.8%		Total cancer mortality stratified by baseline 25(OH)D sextiles		X	X		X	X	
Hutchinson, 2010[79] Tromso Tromso, Norway	• Health status nd • Mean age (SD), y nd • Male (%) nd		Cancer mortality stratified by baseline 25(OH)D quartiles		X	X	X		X	
Lin, 2012[83] Linxian, China	• Health status Healthy, Hyper-tension • Mean age (SD), y 56.5 (SD 7.9) • Male (%) 55%		Cancer mortality stratified by baseline 25(OH)D tertiles		X	X	X		X	
Michaelsson, 2010[84] Uppsala Longitudinal Study of Adult Men Uppsala, Sweden	• Health status More than 1/3 being treated for hypertension • Mean age (SD), y 71 (SD 0.6) • Male (%) 100%		Cancer mortality stratified by baseline 25(OH)D tertiles	X	X	X	X	X	X	
Signorello, 2013[74] Southern Community Cohort Study US	• Health status nd • Mean age (SD), y nd • Male (%) nd					X			X	

Table 15. Vitamin D and total cancer and total cancer mortality: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Schottker 2013[76] ESTHER Germany	• Health status • Mean age • Male (%)	NR 62 (SD 6.5) 43.8%		Cancer mortality stratified by baseline 25(OH)D tertiles	X	X		X	X	X	
Ordonez-Mena[97] Saarland. Germany	• Health status • Mean age • Male (%)	nd NR (50–74) 54%		Cancer mortality stratified by baseline 25(OH)D tertiles	X	X	X			X	
Afzal 2013[99] Denmark	• Health status • Mean age • Male (%)	NR 58 (47–65) NR		Cancer mortality stratified by baseline 25(OH)D category		X	X			X	
New nested case-control studies:											
Fedirko, 2012[101] EPIC Multiple Countries	• Health status • Mean age (SD), y • Male (%)	nd 62.1 (SD 7.2) 40.5%				X	X	X	X	X	

Table 16. Vitamin D and total cancer and total cancer mortality: Results of RCTs [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Followup, y	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Lappe 2007[102] Nebraska, US (41º N) [17556697]	Post-menopausal women	Incident cancer (all causes)	2°	4	Vit D_3 1000 IU + Ca (citrate 1400 mg or carbonate 1500 mg)	13	446	RR (Vit D+Ca vs. Ca)	0.76	0.38, 1.55	NS	B
					Ca (citrate 1400 mg or carbonate 1500 mg)	17	445					
	Post-menopausal women	Incident cancer (restricted to subjects who were free of cancer at 1 y intervention)	2°	4	Vit D_3 1000 IU + Ca (citrate 1400 mg or carbonate 1500 mg)	8	403	RR (Vit D+Ca vs. Ca)	0.55	0.24,1.28	NS	B
					Ca (citrate 1400 mg or carbonate 1500 mg)	15	416					
Trivedi 2003[66] [12609940]	65–85 y, Both sexes	Incident cancer (all causes)	2°	5	Vit D_3 100,000 IU every 4 mo (~833 IU/d)	188	1345	HR (Vit D vs. placebo)	1.09	0.86, 1.36	NS	B
					Placebo	173	1341					
		Total cancer mortality	2°	5	Vit D_3 100,000 IU every 4 mo (~833 IU/d)	63	1345	HR (Vit D vs. placebo)	0.86	0.61, 1.2	NS	
					Placebo	72	1341					

Note: Outcomes cells are shaded for the Control rows.

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
Freedman 2007[103] NHANES III US [16481636]	Adults, both sexes	Cancer mortality (536/16818; 0.032)	105 mo	<50	175	5744	**1**	**Reference**	0.65	B
				50 to <62.5	103	3143	1.22	0.91, 1.64		
				62.5 to <80	117	3713	1.02	0.69, 1.50		
				80 to <100	80	4218 (total, ≥80 nmol/L)	1	0.71, 1.40		
				100 to <120	41		0.92	0.58, 1.46		
				≥120	20		1.49	0.85, 2.64		
	Adults, males	Cancer mortality (318/7632; 0.042)	105 mo	<50	88	1993	**1**	**Reference**	0.08	
				50 to <62.5	57	1461	1.03	0.73, 1.44		
				62.5 to <80	71	1845	0.99	0.57, 1.74		
				80 to <100	58	2333 (total, ≥80 nmol/L)	1.21	0.83, 1.78		
				≥100	44		1.35	0.78, 2.31		
	Adults, females	Cancer mortality (218/9163; 0.024)	105 mo	<50	87	3751	**1**	**Reference**	0.12	
				50 to <62.5	46	1682	1.4	0.94, 2.08		
				62.5 to <80	46	1845	1.02	0.62, 1.67		
				80 to <100	22	1885 (total, ≥80 nmol/L)	0.72	0.40, 1.26		
				≥100	17		0.78	0.40, 1.53		

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
	Adults, both sexes	Cancer mortality (N=13331)	Median 8.7 (IQR 7.1–10.2) y	>80	nd	nd	**1**	**Reference**	nd	C
				61–80	nd	nd	0.8	0.54, 1.19		
				44–60	nd	nd	1.08	0.8, 1.46		
				<44	nd	nd	0.91	0.63, 1.31		
NEW Cohort Studies										
Cawthon 2010[98] MrOS US (6 sites)	Men 65 and over	cancer mortality	7.3 yrs	Q 1: <49.8 nmol/L	NR	372	0.52	0.27, 1.00	0.086	B
				Q 2: 49.8≥ to <63 nmol/L	NR	370	0.90	0.51, 1.60		
				Q 3: ≥63to <75 nmol/L	NR	372	0.80	0.45, 1.41		
				Q 4: ≥75 nmol/L	NR	376	1.00	reference		
				Deficient, <50 nmol/L	NR	376	0.51	0.27, 0.98	0.044	
				Insufficient, 50 to <75 nmol/L	NR	737	0.85	0.52, 1.40		
				Sufficient, ≥75 nmol/L	NR	377	1.00	reference		
				per SD decrease	NR	1490	0.80	0.64, 0.99	NR	
de Boer 2012[87] Cardiovascular Health Study US (4 sites)	Adults 65 and over	cancer	11 yrs	Normal level	259	1126	1.00	Reference	NR	A
				Low level (season specific, ranges 43–61 nmol/L)	111	495	1.13	0.90, 1.42		
Eaton 2011[70] WHI US (multisite)	Postmenopausal women	cancer mortality	10 yrs	Q 1: 3.25–36.50 nmol/L	nd	608	1.39	0.88, 2.19	0.11	A
				Q 2: 36.51–49.95 nmol/L	nd	606	1.22	0.79, 1.89		
				Q 3: 49.96–65.38 nmol/L	nd	608	1.12	0.72, 1.72		
				Q 4: 65.39–146.67 nmol/L	nd	607	1.00	Reference		

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
Freedman 2010[100] NHANES III US (multisite)	men & women, all seasons	total cancer mortality	13.4 yrs	< 37.5 nmol/L	116	2689	RR = 1	Reference	0.43	B
				37.5–<50 nmol/L	174	3056	1.04	0.77, 1.41		
				50–<62.5 nmol/L	165	3143	1.23	0.89, 1.69		
				62.5–80 nmol/L	200	3713	1.19	0.86, 1.65		
				80–<100 nmol/L	139	2521	1.12	0.80, 1.57		
				≥100 nmol/L	90	1697	1.15	0.79, 1.68		
	men & women, winter/lower latitude	total cancer mortality		< 37.5 nmol/L	55	2689	1.00	Reference	0.23	
				37.5–<50 nmol/L	79	3056	1.3	0.77, 2.19		
				50–<62.5 nmol/L	57	3143	1.2	0.64, 2.26		
				62.5–80 nmol/L	78	3713	1.67	0.98, 2.86		
				80–<100 nmol/L	54	2521	1.31	0.77, 2.23		
				≥100 nmol/L	32	1697	1.5	0.74, 3.02		
	men & women, summer/ higher latitude			< 37.5 nmol/L	61	2689	1.00	Reference	0.67	
				37.5–<50 nmol/L	95	3056	0.91	0.63, 1.32		
				50–<62.5 nmol/L	108	3143	1.19	0.78, 1.82		
				62.5–80 nmol/L	122	3713	1.02	0.67, 1.54		
				80–<100 nmol/L	85	2521	1.03	0.66, 1.63		
				≥100 nmol/L	58	1697	1.02	0.63, 1.45		
	men, all seasons			< 37.5 nmol/L	47	2689	1.00	Reference	0.09	
				37.5–<50 nmol/L	95	3056	1.66	0.98, 2.80		
				50–<62.5 nmol/L	90	3143	1.43	0.90, 2.26		
				62.5–80 nmol/L	122	3713	1.52	0.82, 2.80		
				80–<100 nmol/L	90	2521	1.66	1.06, 2.61		
				≥100 nmol/L	69	1697	1.85	1.02, 3.35		
	men, winter/lower latitude			< 37.5 nmol/L	25	2689	1.00	Reference	0.55	
				37.5–<50 nmol/L	51	3056	2.58	1.37, 4.87		
				50–<62.5 nmol/L	31	3143	1.14	0.48, 2.70		
				62.5–80 nmol/L	52	3713	1.99	0.86, 4.13		
				80–<100 nmol/L	33	2521	1.42	0.74, 2.72		
				≥100 nmol/L	23	1697	1.94	0.69, 5.45		

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
	men, summer/higher latitude			< 37.5 nmol/L	22	2689	1.00	Reference	0.045	
				37.5–<50 nmol/L	44	3056	1.28	0.51, 3.23		
				50–<62.5 nmol/L	59	3143	1.55	0.81, 2.99		
				62.5–80 nmol/L	70	3713	1.33	0.53, 3.53		
				80–<100 nmol/L	57	2521	1.76	0.87, 3.57		
				≥100 nmol/L	46	1697	1.84	0.85, 3.98		
	women, all seasons			< 37.5 nmol/L	69	2689	1.00	Reference	0.29	
				37.5–<50 nmol/L	79	3056	0.85	0.59, 1.22		
				50–<62.5 nmol/L	75	3143	1.25	0.82, 1.90		
				62.5–80 nmol/L	78	3713	1.11	0.69, 1.79		
				80–<100 nmol/L	49	2521	0.86	0.50, 1.46		
				≥100 nmol/L	21	1697	0.64	0.35, 1.18		
	women, winter/lower latitude			< 37.5 nmol/L	30	2689	1.00	Reference	0.42	
				37.5–<50 nmol/L	28	3056	0.74	0.36, 1.51		
				50–<62.5 nmol/L	26	3143	1.27	0.51, 3.18		
				62.5–80 nmol/L	26	3713	1.44	0.61, 3.38		
				80–<100 nmol/L	21	2521	1.28	0.50, 3.24		
				≥100 nmol/L	9	1697	1.01	0.26, 3.90		
	women, summer/higher latitude			< 37.5 nmol/L	39	2689	1.00	Reference	0.03	
				37.5–<50 nmol/L	51	3056	0.88	0.54, 1.43		
				50–<62.5 nmol/L	49	3143	1.18	0.65, 2.12		
				62.5–80 nmol/L	52	3713	0.99	0.52, 1.87		
				80–<100 nmol/L	28	2521	0.7	0.34, 1.44		
				≥100 nmol/L	12	1697	0.52	0.25, 1.10		

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
Hutchinson 2010[79] Tromsø Study Norway	Men (55–74 years) Women (50–74 years)			Quartile 1: mean=33.8 (sd=7.6)	72	1184	1.14	0.80–1.63	NR	
non-smokers				Quartile 2: mean=46.7 (sd=6.0)	69	1187	1.13	0.80–1.61		
				Quartile 3: mean=56.2 (sd=6.0)	74	1192	1.23	0.87–1.75		
		cancer mortality	11.7 yrs	Quartile 4: mean=72.3 (sd=13.2)	58	1188	1.00	Reference		B
smokers				Quartile 1: mean=33.8 (sd=7.6)	55	597	0.82	0.56–1.21	NR	
				Quartile 2: mean=46.7 (sd=6.0)	54	606	0.86	0.59–1.26		
				Quartile 3: mean=56.2 (sd=6.0)	60	607	1.02	0.70–1.48		
				Quartile 4: mean=72.3 (sd=13.2)	56	600	1.00	Reference		
Lin 2012[83] General Population Trial of Linxian China				continuous 25(OH)D	217	1101	0.97	0.89, 1.05	0.406	
	Men (40–69 years)	cancer deaths	24 yrs	continuous 25(OH)D	141	608	1.00	0.91, 1.10	0.967	B
	women			continuous 25(OH)D	76	493	0.88	0.75, 1.03	0.115	

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
Michaelsson 2010[84] Uppsala Longitudinal Study of Adult Men Sweden	Elderly men (mean age 71)	cancer mortality	12.7 yrs	< 10th percentile (<46 nmol/L)	27	119	1.99	1.29, 3.08		B
				10th–90th percentile (46–93 nmol/L)	118	956	1.00	Reference		
				>90th percentile (>93 nmol/L)	19	119	1.56	0.95, 2.56		
Signorello 2013[74] Southern Community Cohort Study	Men and women (40–79 years, 2/3 African American)	cancer death	NR	Quartile 4: (>54.1 nmol/L)	115	228	OR = 1	Reference	0.53	A
				Quartile 3: 37.9–>54.1 nmol/L)	102	228	OR = 0.79	0.52, 1.21		
				Quartile 2: (25.45– 37.9 nmol/L)	127	255	OR = 1.03	0.66, 1.59		
				Quartile 1: <25.45 nmol/L)	133	243	OR = 1.28	0.78, 2.11		
Tomson 2013[75] Whitehall study		Death, cancer	13.1 yrs	Doubling Concentration	809	5409	0.84	0.71, 1.00		B
Schottker 2013[76] ESTHER		cancer mortality	9.5 yrs	<30	90	1439	1.42	1.08, 1.87		B
				30–50	172	4188	1.04	0.83, 1.29		
				>50	171	3927	1.00	Reference		
Afzal 2013[99]		all cancer	28 yrs	50% reduction in plasma levels	2488	9791	1.06	1.02, 1.11		B
Ordonez-Mena[97]		total cancer	8 yrs	Q1	235	2253	1.10	0.93, 1.30		B
				Q2+Q3	396	4500	1.00	Reference		
				Q4	242	2254	1.12	0.95, 1.32		
NEW Nested case-control study										
Fedirko 2012[101] EPIC Europe (multinational)	Men and women (age at diagnosis approximately 62)	colorectal cancer specific mortality	73 mos	<36.3	104	242	1.00	Reference	0.04	B
				36.4–48.6	85	239	0.76	0.56, 1.02		
				48.7–60.5	95	241	0.93	0.69, 1.24		
				60.6–76.8	78	240	0.78	0.58, 1.06		
				>76.8	82	240	0.69	0.50, 0.93		

*Statistically significant (P<0.05)

Prostate Cancer

Synopsis

No qualified systematic reviews have evaluated the association between serum 25(OH)D concentrations and incidence of prostate cancer. **In the current report, one prospective cohort study and four nested case control studies (2 rated A, 3 rated B) found no association between baseline serum 25(OH)D concentrations and risk for prostate cancer. Two nested case-control studies (2B) observed a trend between higher serum 25(OH)D concentrations and increasing risk for prostate cancer. In one study this increase was seen only among men whose sera were sampled in Summer or Autumn; in the other study, this trend was observed only when participants were divided by quartiles of serum 25(OH)D concentration, but not when they were divided by categories of vitamin D sufficiency (concentrations less than 50nmol/L being considered deficient, 50–75nmol/L insufficient, and 75–125nmol/L considered sufficient). In the original report,** eight nested case-control studies (2 rated B, 6 C) found no association between baseline serum 25(OH)D concentrations and the risk of prostate cancer. One study rated C found a significant association between lower baseline serum 25(OH)D concentrations (<30 compared to >55 nmol/L) and higher risk of prostate cancer (adjusted OR 1.8, lowest compared to highest quartile). The same study found that the prostate cancer risk was increased in subjects less than 52 years at study entry and who had serum 25(OH)D concentration less than 40 nmol/L (adjusted OR 3.5). However, there was no difference in risk between low and high serum 25(OH)D concentration for those older than 51 years at study entry. A C-rated study suggested a U-shaped association between baseline serum 25(OH)D concentrations and the risk of prostate cancer.

Detailed Presentation (Tables 18 & 19; Figure 7)

For the current report, a total of one prospective cohort and six nested case-control studies reported on the association between baseline serum 25(OH)D concentrations and the risk for prostate cancer.[104-109] The cohort study and four of the six nested case-control studies observed no association between serum 25(OH)D and risk for prostate cancer. No studies identified an association between lower serum 25(OH)D and increasing overall risk for prostate cancer. One study, a nested case-control within the Health Professionals' Followup Study, found an association between lower baseline serum 25(OH)D and increasing risk for lethal prostate cancer (adjusted OR 0.44 [0.24, 0.79) (comparing the lowest with the highest quartile of 25(OH)D), with no effect of time to diagnosis (rated A).[108] Three nested case-control studies (two rated A and one B) observed a trend between higher serum 25(OH)D concentrations and increasing risk for prostate cancer.[105-107] In one study this increase was seen only among men whose sera were sampled in Summer or Autumn;[106] in another study, the Multiethnic Cohort, this trend was observed only when participants were divided by quartiles of serum 25(OH)D concentration, but not when they were divided by categories of vitamin D sufficiency.[107] The number of cases in the nested case control studies ranged from 297 to 2,106. The methodological quality of two studies was B, and four were rated A.

In the original report, a total of 12 nested case-control studies in 14 publications reported on the association between baseline serum 25(OH)D concentrations and the risk of prostate cancer.[103,110-122] The number of cases ranged from 61 to 749. The latitudes of the studies ranged

from 21º N to 60º N. The mean age of the subjects ranged from 44 to 68 years. Baseline serum concentrations of 25(OH)D in these studies ranged from 12.8 to 194 nmol/L. The time between blood drawn and the diagnosis of prostate cancer varied from 2 to 16 years. The methodological quality of three studies was rated B and nine studies were rated C.

Ten studies **identified for the original report** reported data on subjects with a mean age ranged from 51 to 68 years. Eight studies did not find an association by trend analysis between baseline serum 25(OH)D concentrations and the risk of prostate cancer.[110,112-119,122] One study found no association between baseline serum 25(OH)D concentrations and mortality from prostate cancer.[114] One study found an association between lower baseline serum 25(OH)D concentrations (<30 compared to >55 nmol/L) and the risk of prostate cancer (P for trend = 0.01).[111] The adjusted OR of the lowest compared to highest quartile was 1.8. The study also found that the prostate cancer risk was increased in subjects less than 52 years at study entry and had low serum 25(OH)D concentration (≤40 nmol/L) (adjusted OR 3.5, 95% CI 1.7, 7.0). However, there was no difference in risk (adjusted OR 1.2, P=NS) between low (≤40 nmol/L) and high (>40 nmol/L) serum 25(OH)D concentration for those older than 51 years at study entry. This study did not adjust for factors potentially relevant to prostate cancer. One study reported an U-shaped association between baseline serum 25(OH)D concentrations and the risk of prostate cancer: the odds ratio in the group with 25(OH)D concentration of at least 80 nmol/L was 1.7 (95% CI 1.1, 2.4) compared to the group with a 25(OH)D concentration of 40–49 nmol/L; the odds ratio in the group with 25(OH)D concentration of no more than 19 nmol/L was 1.5 (95% CI 0.8, 2.7) compared to the group with a 25(OH)D concentration of 40 to 49 nmol/L.[120] Even though this study used a conditional logistic regression in its analysis to maintain matching status, it was unclear if additional factors potentially relevant to prostate cancer were also entered into the regression analysis.

$1,25(OH)_2D$

Five studies reported on the association between $1,25(OH)_2D$ serum concentrations and the risk of prostate cancer. Four studies did not find an association.[115,118,119,122] One study found that the risk of prostate cancer decreased with higher serum concentrations of $1,25(OH)_2D$ in men with low serum concentrations of 25(OH)D (unadjusted OR 0.15, comparing 4th quartile of $1,25(OH)_2D$ (104–211 pmol/L) to 1st quartile (13–68 pmol/L) in men with serum 25(OH)D concentrations that ranged from 7.5–45 nmol/L).[114] When stratified by age and race, this association was only found in men above the median age of 57 years at time of blood drawn but not in younger men; the association was similar in black and white men.

Findings by Life Stage

- **0–6 mo**
  not applicable
- **7 mo–2 y**
  not applicable
- **3–8 y**
  not applicable
- **9–18 y**
  not reviewed
- **19–50 y**
  None of the studies in the update report focused on younger participants. Two

studies **in the original report** provided data on younger subjects. Ahonen et al. analyzed subjects from 40 to 57 years of age.[111] The study found that the prostate cancer risk was increased in subjects less than 52 years at study entry and had low serum 25(OH)D concentration (≤40 nmol/L) (adjusted OR 3.5, 95% CI 1.7, 7.0). The corresponding adjusted OR for those older than 51 years at study entry was 1.2 and was not significant. This study adjusted for factors related to insulin resistance syndrome but not those potentially related to prostate cancer. Freedman et al. analyzed data from NHANES III and reported on subjects with a mean age of 44 years and found that the adjusted relative risk of mortality from prostate cancer was 0.91 (95% CI 0.39, 2.14) in the group with baseline serum 25(OH)D concentration of at least 62.5 nmol/L compared to the group with less than 62.5 **nmol/L.**[103] **In the original report,** one study found that the prostate cancer risk was highest in subjects less than 52 years at study entry and had low serum 25(OH)D concentration (≤40 nmol/L) (adjusted OR 3.5, 95% CI 1.7, 7.0). Another study analyzed data from NHANES III and reported on subjects with a mean age of 44 years and found that the adjusted relative risk of mortality from prostate cancer was 0.91 (95% CI 0.39, 2.14) in the group with baseline serum 25(OH)D concentration of at least 62.5 nmol/L compared to the group with less than 62.5 nmol/L.

- **51–70 y**
  All of the studies identified for the update report included men whose average age was 60 or higher. One cohort included only men 65 and older[104] Only one study reported on effect of age at diagnosis. No studies identified an association between lower serum 25(OH)D and increasing overall risk for prostate cancer. One study, a nested case-control within the Health Professionals' Followup Study, found an association between lower baseline serum 25(OH)D and increasing risk for lethal prostate cancer (adjusted OR 0.44 [0.24, 0.79) (comparing the highest to the lowest quartile of 25(OH)D), with no effect of time to diagnosis.[108] Three nested case-control studies (2B) observed a trend between higher serum 25(OH)D concentrations and increasing risk for prostate cancer.[105-107] In one study this increase was seen only among men whose sera were sampled in Summer or Autumn;[106] in another study, the Multiethnic Cohort, this trend was observed only when participants were divided by quartiles of serum 25(OH)D concentration, but not when they were divided by categories of vitamin D sufficiency.[107] In the original report, eight studies did not find an association by P for trend analysis between baseline serum 25(OH)D concentrations and the risk of prostate cancer. One study found an inverse association of baseline serum 25(OH)D concentrations (<30 compared to >55 nmol/L) and the risk of prostate cancer (adjusted OR 1.8, lowest compared to highest quartile, P for trend = 0.01). This study found that the prostate cancer risk was increased in subjects less than 52 years at study entry and had low serum 25(OH)D concentration (≤40 nmol/L) (adjusted OR 3.5, 95% CI 1.7, 7.0). However, there was no difference in risk (adjusted OR 1.2, P=NS) between low (≤40 nmol/L) and high (>40 nmol/L) serum 25(OH)D concentration for those older than 51 years at study entry. One study reported an U-shaped association between baseline serum 25(OH)D concentrations and the risk of prostate cancer: the odds ratio in the group with 25(OH)D concentration of at least 80 nmol/L was 1.7 (95% CI 1.1, 2.4) compared to the group with a 25(OH)D concentration of 40–49 nmol/L; the odds ratio in the group with 25(OH)D concentration of no more

than 19 nmol/L was 1.5 (95% CI 0.8, 2.7) compared to the group with a 25(OH)D concentration of 40 to 49 nmol/L.

- **≥71 y**
  No study specifically targeted men older than 70 years.
- **Postmenopause**
  Not applicable
- **Pregnant & lactating women**
  Not applicable

Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV Exposure	Lifestyles	
Ahn 2008[110] PLCO US (21ºN to 44ºN) [18505967]	Health status	8% current smoker	Assay	RIA (Heartland)	Prostate cancer risk stratified by baseline 25(OH)D quintiles	X		X	X		X	
	Mean age (range/SD), y	67.8 (5.3)										
	Male (%)	100	Season blood drawn	nd								
Platz 2004[119] Mikhak 2007[117] HPFS US (multiple latitudes) [15090720] [17440943]	Health status	Smoked 18%; DM 3.6%	Assay	RIA	Prostate cancer risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	6% nonwhite
	Mean age (range/SD), y	66 (7)										
	Male (%)	100	Season blood drawn	nd								
Freedman 2007[103] NHANES III US (multiple latitudes) [17971526]	Health status	28% current smoker	Assay	RIA	Prostate cancer mortality stratified by 2 baseline 25(OH)D categories	X	X	X	X	X	X	71% white; 14% black; 6% Hispanics
	Mean age (range/SD), y	44										
	Male (%)	100	Season blood drawn	South: Nov to Mar; North: Apr to Oct								
Tuohimaa 2004[120] Helsinki Heart Vasterbotten; Janus Project; Finland (60°N) [14618623]	Health status	Gemfibrozil vs. placebo subjects	Assay	RIA (Incstar)	Prostate cancer risk stratified by 5 baseline 25(OH)D categories		X			X		
	Mean age (range/SD), y	<40 to >60										
	Male (%)	100	Season blood drawn	nd								

Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV Exposure	Lifestyles	
Li 2007[116] Gann 1996[122] PHS US (multiple latitudes) [17388667] [8850273]	Health status Mean age (range/SD), y Male (%)	on ASA, β-carotene, placebo trial; 9% current smoker 58.9 (8.3) 100	Assay Season blood drawn	RIA (Bruce Hollis) 24% spring or winter	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X				X	94% white
Corder 1993[114] San Francisco US (37ºN) [8220092]	Health status Mean age (range/SD), y Male (%)	nd 57 (38–81) 100	Assay Season blood drawn	Competitive protein-binding (Haddad, 1971) nd	Prostate cancer risk compared by baseline 25(OH)D		X			X		50% black; 50% white
Ahonen 2000[111] Helsinki Heart Finland (60°N) [11075874]	Health status Mean age (range/SD), y Male (%)	Gemfibrozil vs. placebo subjects 40–57 100	Assay Season blood drawn	RIA (Incstar) Jan-Feb; Mar-May; Sep	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X	X	X	X	X	
Nomura 1998[118] Honolulu Heart US (21ºN) [9794175]	Health status Mean age (range/SD), y Male (%)	64% smoked 58 (49–70) 100	Assay Season blood drawn	Protein-binding nd	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X			X	X	100% Japanese Americans
Tuohimaa 2007[121] Helsinki Heart Finland (60°N) 17301263	Health status Mean age (range/SD), y Male (%)	Gemfibrozil vs. placebo subjects 51 (3.7) 100	Assay Season blood drawn	RIA (Incstar) Most in winter	Prostate cancer risk stratified by 3 baseline 25(OH)D categories		X	X	X			

Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted: Nutrients	Demographic	Anthrop	Medical	UV Exposure	Lifestyles	Comments
Jacobs 2004[115] NPC Eastern US (25º46'N to 41ºN) [15225833]	Health status	Selenium vs. placebo subjects[A]	Assay	RIA	Prostate cancer risk stratified by baseline 25(OH)D tertiles		X	X	X	X	X	
	Mean age (range/SD), y	68 (nd)										
	Male (%)	100	Season blood drawn	nd								
Braun 1995[113] WCC, MD US (39°N) [7612803]	Health status	nd	Assay	RIA (Bruce Hollis, 1993)	Prostate cancer risk stratified by baseline 25(OH)D quintiles		X					100% white
	Mean age (range/SD), y	<45–75+										
	Male (%)	100	Season blood drawn	Aug through Nov								
Baron 2005[112] CPP US (multiple latitudes) [15767334][B]	Health status	had >1 colon adenoma removal	Assay	Competitive protein-binding (Quest)	Prostate cancer risk stratified by baseline 25(OH)D tertiles	X	X			X		5% black
	Mean age (range/SD), y	62 (8.7)										
	Male (%)	100	Season blood drawn	nd								
Braun 1995[113] WCC, MD US (39°N) [7612803]	Health status	nd	Assay	RIA (Bruce Hollis, 1993)	Prostate cancer risk stratified by baseline 25(OH)D quintiles		X					100% white
	Mean age (range/SD), y	<45–75+										
	Male (%)	100	Season blood drawn	Aug through Nov								
Baron 2005[112] CPP US (multiple latitudes) [15767334][B]	Health status	had >1 colon adenoma removal	Assay	Competitive protein-binding (Quest)	Prostate cancer risk stratified by baseline 25(OH)D tertiles	X	X			X		5% black
	Mean age (range/SD), y	62 (8.7)										
	Male (%)	100	Season blood drawn	nd								

Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demographic	Anthrop	Medical	UV Exposure	Lifestyles	
New nested case-control studies											
Barnett, 2010[104] MrOS US (various)	Health status Mean age (range/SD), y Male (%)	nd 73.6 (5.9) 100%		Prostate cancer risk stratified by baseline 25(OH)D quartiles		X			X	X	probably need to check another article from this study to get funding info
Brandstedt, 2012[105] Malmo, Sweden	Health status Mean age (range), y Male (%)	nd 61.7 (NR, SD 6.4) 100%		Prostate cancer risk stratified by baseline 25(OH)D quartiles		X	X			X	Malmo Diet and Cancer Study (MDCS)
Meyer, 2013[106] Norway	Health status Mean age (range), y Male (%)	nd 48.2 (SD 9.2) 100%		Prostate cancer risk stratified by baseline 25(OH)D sextiles		X			X		
Park, 2010[107] Multiethnic Cohort Study	Health status Mean age (SD), y Male (%)	nd 68.7 (SD 7.2) 100%		Prostate cancer risk stratified by baseline 25(OH)D quartiles	X		X				
Shui, 2012[108] Health Professionals' Followup Study US	Health status Mean age (SD), y Male (%)	nd 64.4 (SD 7.8) 100%		Prostate cancer risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	
Travis 2009[109] European Prospective Investigation into Cancer and Nutrition (EPIC) Multiple Countries	Health status Mean age (SD), y Male (%)	nd 60.5 (SD 6.2) 100%		Prostate cancer risk stratified by baseline 25(OH)D		X	X			X	

Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demographic	Anthrop	Medical	UV Exposure	Lifestyles	
NEW Cohort study											
Ordonez-Mena 2013[97] ESTHER Saarland, Germany	Health status Mean age Male (%)	NR 50–74 54%		Cancer mortality stratified by baseline 25(OH)D tertiles	X		X	X			confounders-add multivitamin use, fish consumption, red meat consumption, daily fruit intake, daily vegetable intake, scholarly education, physical activity, family history of cancer

[A]For prevention of recurrence of non-melanoma skin cancer.
[B]This is a cohort study, not a nested case-control study.

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report)

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Controls)	Time To Diagnosis, y	25(OH)D Concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
Ahn 2008[110] PLCO [8505967]	51–70	Prostate cancer (741; 781)	2–8	12.8–42.5	119	157	**1**	**Reference**	0.2	B
				42.5–51.	125	156	1.1	0.78, 1.56		
				51.4–60.5	190	157	1.53	1.10, 2.13*		
				60.6–71.7	167	156	1.33	0.95, 1.86		
				71.8–129.5	148	155	1.18	0.83, 1.68		
Platz 2004[119] Mikhak 2007[117] HPFS [15090720] [17440943]	51–70	Prostate cancer (460; 460)	2.2 (mean)	Quartile 1[A]	109	114	**1**	**Reference**	0.59	B
				Quartile 2	115	113	1	0.67, 1.49		
				Quartile 3	94	120	0.77	0.51, 1.15		
				Quartile 4	142	113	1.19	0.79, 1.79		
Freedman 2007[103] NHANES III [17971526]	19–50	Mortality prostate cancer	nd	<62.5	22	nd	**1**	**Reference**	0.95	B
				≥62.5	25	nd	0.91	0.39, 2.14		
Tuohimaa 2004[120] Helsinki Heart [14618623]	19–50 51–70	Prostate cancer (622; 1451)	≤9–>14 (range)	≤19	19	nd	1.5	0.8, 2.7		C
				20–39	169	nd	1.3	0.98, 1.6		
				40–59	229	nd	**1**	**Reference**		
				60–79	138	nd	1.2	0.9, 1.5		
				≥80	67	nd	1.7	1.1, 2.4*		
Li 2007[116] PHS [17388667]	19–50 51–70	Prostate cancer (492; 664)	11 (median)	Quartile 1[B]	nd	nd	1.01	0.71, 1.44	0.91	C
				Quartile 2	nd	nd	1.26	0.89, 1.80		
				Quartile 3	nd	nd	1	0.71, 1.41		
				Quartile 4	nd	nd	**1**	**Reference**		

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Controls)	Time To Diagnosis, y	25(OH)D Concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
Gann 1996[122] PHS [8850273]	19–50 51–70	Prostate cancer (232; 414)	6 (mean)	15.7–53.3	nd	nd	1	nd	0.82	C
				53.4–70.9	nd	nd	1.1	nd		
				71–93.5	nd	nd	1.16	nd		
				93.6–194	nd	nd	0.92	0.56, 1.50		
		Prostate cancer; age ≤61 y		15.7–53.3	nd	nd	1	nd	nd	
				53.4–70.9	nd	nd	1.19	nd		
				71–93.5	nd	nd	1.75	nd		
				93.6–194	nd	nd	1.48	0.73, 2.98		
		Prostate cancer; age >61 y		15.7–53.3	nd	nd	1	nd	nd	
				53.4–70.9	nd	nd	1	nd		
				71–93.5	nd	nd	0.82	nd		
				93.6–194	nd	nd	0.76	0.39, 1.47		
Corder 1993[114] [8220092]	19–50 51–70	Prostate cancer (181; 181)	>5 (mode)	60.0 (case) vs. 50.5 (control) (est.)	181	181	-	-	-	C
		Mortality prostate cancer		nd	51	nd	-	-	-	
Ahonen 2000[111] Helsinki Heart [11075874]	19–50 51–70	Prostate cancer (149; 566)	8–14 (mode)	< 30[C]	48	131	1.8	1.0, 3.2*	0.01	C
				31–40	41	143	1.4	0.8, 2.4		
				41–54	26	148	0.8	0.5, 1.5		
				> 55	34	144	**1**	**Reference**		
		Prostate cancer in those <52 years old at entry		≤40	nd	nd	3.5	1.7, 7.0*		
				>40	nd	nd	1			
		Prostate cancer in those >51 years old at entry		≤40	nd	nd	1.2	0.7, 2.1		
				>40	nd	nd	1			
Nomura 1998[118] Honolulu Heart [9794175]	19–50 51–70	Prostate cancer (136; 136)	16 (mean)	<85[D]	38	34	**1**	**Reference**	0.68	C
				85–101	35	36	0.8	0.4, 1.8		
				102–119	30	32	0.8	0.4, 1.7		
				≥120	33	34	0.8	0.4, 1.8		

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Controls)	Time To Diagnosis, y	25(OH)D Concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
Tuohimaa 2007[121] Helsinki Heart [17301263]	19–50 51–70	Prostate cancer (132; 456)	10.8 (mean)	<40	-	-	1.88	1.15, 3.08*		C
				40–59	-	-	**1**	**Reference**		
				≥60	-	-	1.25	0.64, 2.43		
Jacobs 2004[115] NPC [15225833]	51–70	Prostate cancer (83; 166)	5.1 (mean)	20–63.3	26	58	**1**	**Reference**	0.51	C
				63.4–81.9	33	49	1.71	0.68, 4.34		
				82–149	24	59	0.75	0.29, 1.91		
Braun 1995[113] WCC [7612803]	19–50 51–70	Prostate cancer (61; 122)	14 (mean)	<60.1	7	24	**1**	**Reference**	0.6	C
				60.1–73.8	17	25	2.3	0.7, 7.8		
				73.9–88.5	16	24	2.3	0.7, 7.7		
				88.6–103	4	25	0.6	0.1, 2.5		
				>103	17	24	2.4[E]	0.8, 8.2		
Baron 2005[112] CPP [15767334][F]	19–50 51–70	Prostate cancer (70 cases in a total of 672)[F]	<4 (34%)	<62.9	nd	NA	**1**	**Reference**	0.7	C
				62.9–84.9	nd	NA	1.22	0.66, 2.26		
				85	nd	NA	0.32	0.72, 2.43		
NEW nested case-control studies										
Barnett 2010[104] MrOS	men 65 and over	Prostate Cancer (297 cases in a total of 1648)	NR	Quartile 1(7.75–49.75 nmol/L)	68	411	HR=1.00	**Reference**		B
				Quartile 2(50.0–62.3 nmol/L)	91	415	1.35	0.91, 2.01	0.130	
				Quartile 3(62.5–74.8 nmol/L)	53	406	0.64	0.41, 1.00	0.050	
				Quartile 4 (75–189.0 nmol/L)	85	416	1.20	0.81, 1.78	0.370	
Brandstedt 2012[105]	51–70 yrs; ≥71 yrs	Prostate Cancer (918; 924)	NR	Quartile 1(≤68nmol/L)	206	242	1.00	**Reference**		A
				Quartile 2(69–84nmol/L)	237	232	1.25	0.95, 1.65		
				Quartile3(85–102nmol/L)	245	226	1.37	1.03, 1.82		
				Quartile 4(≥103nmol/L)	230	224	1.34	0.99, 1.82	0.048	

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Controls)	Time To Diagnosis, y	25(OH)D Concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
Meyer 2013[106]		Prostate Cancer (2106;2106)	NR	<30nmol/L	72	92	IRR=0.82	0.58, 1.15		B
				30–49nmol/L	528	553	1.02	0.87, 1.21		
				50–69nmol/L	718	771	1.00	**Reference**		
				70–89nmol/L	537	466	1.24	1.05, 1.47		
				≥90nmol/L	251	224	1.17	0.93, 1.48		
				30–nmol/L increase	NR	NR	1.13	1.02, 1.25		
		Prostate Cancer (Winter/Spring)		<30nmol/L	49	63	0.80	0.52, 1.23		
				30–49nmol/L	304	286	1.09	0.86, 1.40		
				50–69nmol/L	288	297	1.00	**Reference**		
				70–89nmol/L	145	128	1.14	0.85, 1.53		
				≥90nmol/L	38	50	0.74	0.46, 1.18		
				30–nmol/L increase	NR	NR	0.97	0.83, 1.14		
		Prostate Cancer (Summer/Autumn)		<30nmol/L	13	14	0.97	0.45, 2.10		
				30–49nmol/L	132	172	0.87	0.66, 1.16		
				50–69nmol/L	296	329	1.00	**Reference**		
				70–89nmol/L	297	259	1.34	1.05, 1.71		
				≥90nmol/L	180	144	1.46	1.07, 2.00		
				30-nmol/L increase	NR	NR	1.25	1.08, 1.45		
Park 2010[107] multiethnic cohort	Men 45–75 yrs	Prostate Cancer (329, 656)	NR	Quartile 1:<57.3 nmol/L	82	163	1.00	**Reference**		A
				Quartile 2: 57.3 <77.5 nmol/L	84	166	1.05	0.70, 1.58		
				Quartile 3: 77.5<99.8 nmol/L	72	172	0.81	0.52, 1.28		
				Quartile 4: ≥99.8 nmol/L	91	155	1.17	0.72, 1.89	0.600	
				Deficient: <50nmol/LL	53	106	1.10	0.68, 1.78		
				Insufficient: 50–75 nmol/L	98	204	1.04	0.73, 1.48		
				75–125 nmol/L	137	287	1.00	**Reference**		
				≥125 nmol/L	41	59	1.52	0.92, 2.51	0.320	

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report) (continued)

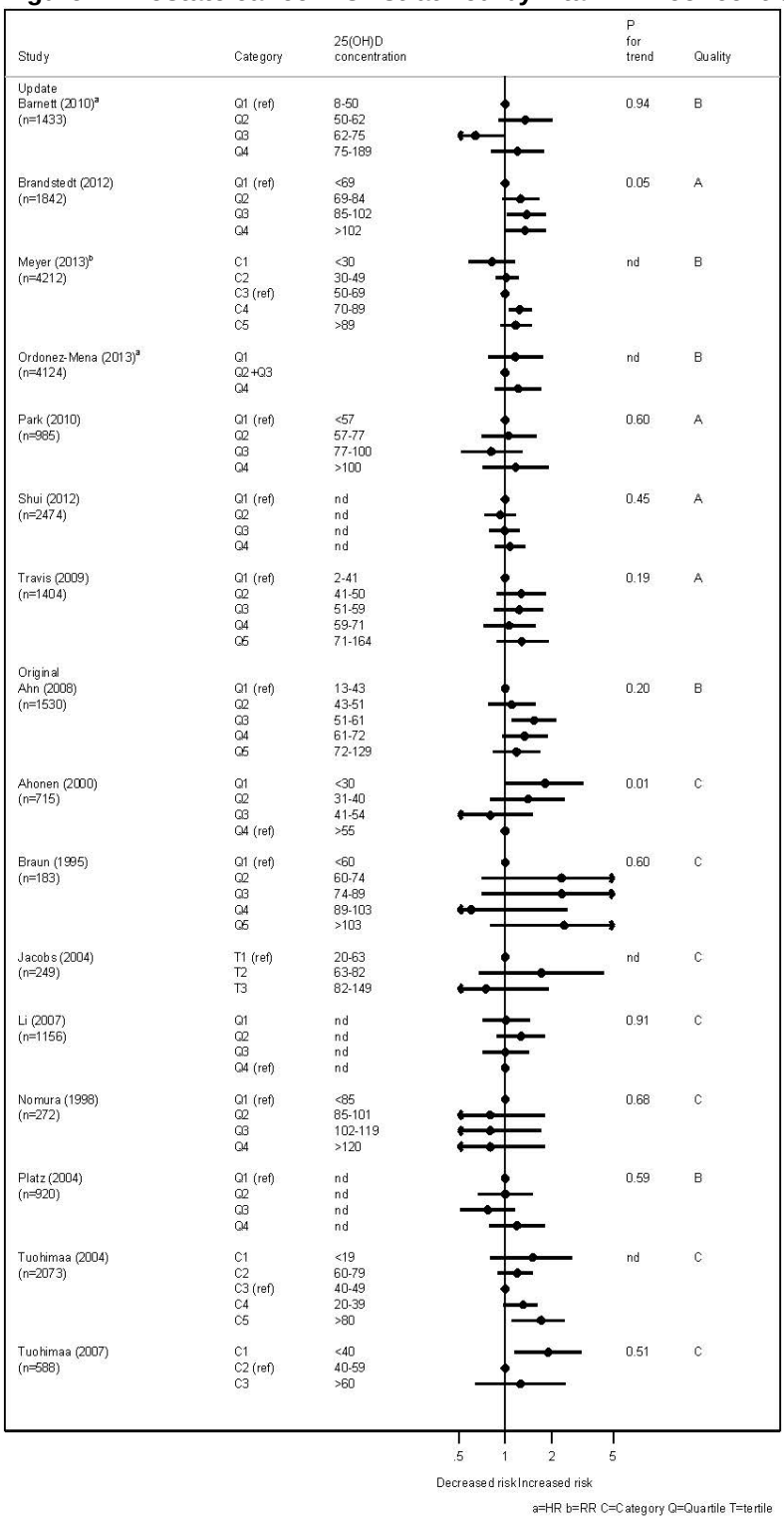
Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Controls)	Time To Diagnosis, y	25(OH)D Concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
Shui 2012[108]				Quartile 1	41	325	1.00	**Reference**		A
Health Professionals' Followup Study		Lethal Prostate Cancer (209;1324)	5.2 years	Quartile 2	33	336	0.78	0.47, 1.30		
				Quartile 3	21	334	0.50	0.28, 0.88		
				Quartile 4	19	329	0.44	0.24, 0.79	0.002	
		Overall Prostate Cancer (1260;1324)	5.2 years	Quartile 1	310	325	1.00	**Reference**		A
				Quartile 2	298	336	0.93	0.74, 1.17		
				Quartile 3	319	334	0.99	0.79,1.24		
				Quartile 4	333	329	1.07	0.86, 1.34	0.45	
		Advance stage at Diagnosis (166;1324)	5.2 years	Quartile 1	51	325	1.00	**Reference**		
				Quartile 2	43	336	0.96	0.61, 52		
				Quartile 3	32	334	0.63	0.39, 1.03		
				Quartile 4	40	329	0.85	0.53, 1.35	0.22	
		High Grade Prostate Cancer (239;1324)	5.2 years	Quartile 1	69	325	1.00	**Reference**		
				Quartile 2	55	336	0.81	0.54, 1.21		
				Quartile 3	51	334	0.75	0.50, 1.13		
				Quartile 4	64	329	0.99	0.67, 1.46	0.87	
Travis 2009[109]		Prostate Cancer	4.1 years	Quintile 1 (2.5–40.4nmol/L)	125	151	1.00	**Reference**		A
European Prospective Investigation into Cancer and Nutrition (EPIC)				Quintile 2(40.5–50.4 nmol/L)	143	150	1.27	0.89, 1.81		
				Quintile 3(50.5–59.1nmol/L)	128	151	1.23	0.85, 1.76		
				Quintile 4 (59.2–70.8nmol/L)	114	150	1.06	0.73, 1.55		
				Quintile 5(70.9–163.7nmol/L)	142	150	1.28	0.88, 1.88		
				Doubling Concentration	652	752	1.17	0.93, 1.47	0.188	

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Controls)	Time To Diagnosis, y	25(OH)D Concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
Ordonez-Mena 2013[97] ESTHER		Prostate Cancer	8 yrs	Q1	38	882	HR 1.16	0.78, 1.74		B
				Q2+Q3	66	1737	HR 1.00	**Reference**		
				Q4	67	1505	HR 1.21	0.86, 1.70		

*Statistically significant (P<0.05)
[A]Cut points separated by analytical run; season, distributions among control (see Table 3 in original study).
[B]Cut points based on control standardized by season of collection.
[C]Cut points based on total original cohort.
[D]Cut points based on control frequency.
[E]Unadjusted.
[F]This is a cohort study, not a nested case-control study.

Figure 7. Prostate cancer risk stratified by vitamin D concentration (updated from original report)



Colorectal Cancer

Synopsis

No qualified systematic reviews have evaluated the association between 25(OH)D concentrations and colorectal cancer mortality or incidence. **No new RCTs and cohort studies that addressed the effect of vitamin D or vitamin D and calcium on colorectal cancer mortality or incidence were identified for the current report. Three nested case-control studies (2A, 1B) found trends of increasing colorectal cancer incidence with decreasing 25(OH)D concentrations. One nested case-control study (rated B) found no association between colorectal cancer and 25(OH)D. Two of these nested case-control studies (2B) also examined colon and rectal cancer as separate outcomes. One study reported a significant negative trend between 25(OH)D and colon cancer risk and the other found a non-significant negative trend. For rectal cancer, the same two studies reported either a negative trend or a small but non-significant negative trend with 25(OH)D.**

In the original report, one B quality RCT of elderly population reported no significant difference in colorectal cancer mortality or incidence between supplemental vitamin D_3 and no supplements. One B quality cohort study found an inverse association between higher 25(OH)D concentrations and the risk of colorectal cancer mortality (HR 0.28, highest compared to lowest tertile). Two B quality nested case-control studies of women found a trend between higher 25(OH)D serum concentrations and lower risk of colorectal cancer incidence (trend analysis). Another two B quality nested case-control studies of men, and one B quality and two C quality nested case-control studies of both sexes reported no significant association between 25(OH)D concentrations and risk of colorectal cancer or colon cancer.

Detailed Presentation of Supplemental Vitamin D and Colorectal Cancer (Tables 20 & 21)

In the original report, an RCT compared supplemental vitamin D_3 (100,000 IU every 4 months) with placebo in 2686 elderly participants with a mean age of 75 years in the United Kingdom (latitude 52° N).[66] Colorectal cancer mortality and incidence were evaluated as two of multiple secondary endpoints. The primary endpoint was the prevention of fracture. At 5 years vitamin D_3 supplementation had no significant effect on the prevention of colorectal cancer mortality (P=0.33) or incidence (P=0.94). This trial was rated B because it did not report in sufficient detail the randomization method, and the outcome ascertainment was based on death certificates or self-reported data, not verified with another objective documents (e.g., medical records or pathology reports).

Findings per Age and Sex

The same British trial reported no significant difference in colorectal cancer mortality or incidence between the vitamin D supplements group and the placebo at 5 years in men (P=0.96 and 0.59, respectively). In women, the trial also found no significant difference in colorectal cancer incidence between the two groups (P=0.32), whereas the risk of colorectal cancer mortality in the supplements group was significantly decreased compared to the placebo (0/326 deaths vs. 4/323 deaths; HR, not reported; P=0.04).

Findings per Special Populations

No subgroup data were available regarding special populations (e.g., obese participants, smokers, ethnic groups, or users of contraceptives).

Table 20. Vitamin D and colorectal cancer: Characteristics of RCTs [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Trivedi 2003[66] Oxford, UK (52°N) [12609940]	• Health status • Mean age (range), y • Male (%)	General population 75 (65–85) 76%	25(OH)D: 53.4 nmol/L Calcium intake= 742 mg/day (at 4 years, no difference by treatment allocation)	Vit D_3 100,000 IU vs. placebo every 4 months	Participants taking ≥80% of study medication: 76%[A]	Previous CVD: 28%, previous cancer: 6%, steroids user: 5%, and HRT taker: 7%

Abbreviations: CVD = cardiovascular disease; HRT = hormone replacement therapy.
[A]No difference between the vitamin D and the placebo arm.

Table 21. Vitamin D and colorectal cancer: Results of RCTs [no new studies in the current report]

Author Year Study Name [PMID]	Age Range, Sex (Subgroup)	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Trivedi 2003[66] [12609940]	65–85 y, Both sexes	CRC, mortality	2°	5 y	Vit D_3 100,000 IU every 4 mo	7	1345	Age adj HR (Vit D/Placebo)	0.62	0.24, 1.60	0.33	B
					Placebo	11	1341					
		CRC, incidence	2°		Vit D_3	28	1345	Age adj HR (Vit D/Placebo)	1.02	0.60, 1.74	0.94	
					Placebo	27	1341					
	65–85 y, Men	CRC, mortality	2°	5 y	Vit D_3	7	1019	Age adj HR (Vit D/Placebo)	0.97	0.34, 2.78	0.96	
					Placebo	7	1018					
		CRC, incidence	2°		Vit D_3	25	1019	Age adj HR (Vit D/Placebo)	1.18	0.65, 2.12	0.59	
					Placebo	21	1018					
	65–85 y, Women	CRC, mortality	2°	5 y	Vit D_3	0	326	Age adj HR (Vit D/Placebo)	NA	NA	0.04	
					Placebo	4	323					
		CRC, incidence	2°		Vit D_3	3	326	Age adj HR (Vit D/Placebo)	0.49	0.12, 1.98	0.32	
					Placebo	6	323					

Note: Outcomes cells are shaded for the Control rows.

Detailed Presentation of 25(OH)D Concentrations and Colorectal Cancer (Tables 22 & 23; Figures 8, 9, & 10)

Four nested case-control studies that assessed the association of serum 25(OH)D with colorectal cancer were identified for the current report. A nested case-control study conducted within the EPIC study that matched 1220 cases of colorectal cancer with 1222 controls found increasing risk for colorectal cancer with lower serum 25(OH)D.[123] This study was rated B for quality because cases were ascertained from cancer registries and were not verified independently. Two additional nested case-control studies, one nested in the Women's Health Initiative (WHI) and the other in the Multiethnic Cohort (both rated A), found increasing risk for colorectal cancer with lower 25(OH)D (the WHI is described further later in the section on vitamin D plus calcium).[124,125] Another case-control study, nested in the Physicians' Health Study, found no association between colorectal cancer incidence and levels of 25(OH)D and 1,25(OH)2D in U.S. male physicians aged 40–84 years (rated B).[126]

The studies nested in the EPIC and Physicians' Health cohorts also assessed colon and rectal cancer as separate outcomes. The nested case-control study within EPIC found a trend toward increasing risk for colon cancer incidence with lower 25(OH)D;[123] the study within the Physicians' Health cohort found a similar but non-significant trend.[126] For rectal cancer incidence, the Physicians' Health nested case-control study found a negative trend between 25(OH)D and rectal cancer, while the EPIC nested case-control found a small but non-significant negative trend.

From the original report, a total of seven nested case-control studies evaluated the associations between 25(OH)D concentrations and risk of colorectal cancer[127-131] or colon cancer.[132,133] The number of pairs of cases and controls in these studies ranged from 101 to 588. Another cohort study comprising 16,818 adult community volunteers from the NHANES III[103] assessed the association between 25(OH)D concentrations and colorectal cancer mortality. The mean age of the subjects ranged from 44 to 66 years. Locations of the studies ranged from 20°N to 60°N. Baseline 25(OH)D concentrations ranged from 10 nmol/L to 227.5 nmol/L. No studies reported follow up 25(OH)D concentrations. Time between blood drawn and the diagnosis of colorectal cancer incidence or mortality ranged from less than 1 year to 17 years. None of the studies reported power calculations. Methodological quality of five nested case-control studies[127-131] were rated B and two were rated C.[132,133] Common reasons for downgrading the quality ratings included exclusion of participants without available blood samples, no verification of cancer diagnosis, and lack of adequate statistical adjustments. The cohort study[103] was rated B because it was unclear whether cases were verified and there was no statistical adjustment for family history.

Findings per Age and Sex

The NHANES III[103] analyzed data for both sexes combined. An adjusted analysis found an inverse association between 25(OH)D concentrations and the risk of colorectal cancer mortality (HR: 0.28, highest [≥80 nmol/L] compared to lowest tertile [<50 nmol/L]; P for trend = 0.02). Two studies from WCC reported colon cancer incidence for both sexes combined.[132,133] One study reported a significantly lower 25(OH)D concentrations in colon cancer cases than controls (58.9 nmol/L vs. 86.6 nmol/L; P<0.001).[133] Both studies reported no significant association between 25(OH)D concentrations and colon cancer risk by trend analysis.

In the original report, three studies, from the Japan PHC, HPFS, and ATBC respectively, provided data on adult men.[127-129] None of the studies found an association between 25(OH)D concentrations and colorectal cancer risk. Although all three studies provided data on colon cancer and rectal cancer as subgroup analysis, only HPFS reported a significant trend between higher 25(OH)D concentrations and lower risk of colon cancer (OR 0.46, highest [median 97.0 nmol/L] compared to lowest quartile [median 48.3 nmol/L]; P for trend = 0.005).[129] The HPFS also reported a subgroup analysis on men aged 65 years or older.[129] No significant association was reported between 25(OH)D concentrations and colorectal cancer risk by trend analysis.

The Japan PHC and HPFS compared 25(OH)D concentrations between colorectal cancer cases and controls.[128,129] Neither reported a significant difference. One study explored subgroup analyses. Only the rectal cancer cases had significantly lower 25(OH)D concentrations compared to the controls (55 nmol/L for cases vs. 110 nmol/L for controls; P = 0.005).[128]

Two nested case-control studies from the NHS and Japan PHC provided data on adult women.[128,130] The NHS reported a trend between higher 25(OH)D concentrations and lower colorectal cancer risk (OR 0.53, highest [median 99.1 nmol/L] compared to lowest quintile [median 40.2 nmol/L]; P for trend = 0.02).[130] This trend remained significant in a subgroup analysis of women age 60 years or older (OR 0.35 between the highest quintiles [median 99.1 nmol/L] and lowest [median 40.2 nmol/L]; P for trend = 0.006) or in rectal cancer alone (OR 0.31, highest [median 92.4 nmol/L] compared to lowest tertile [median 44.4 nmol/L]; P for trend = 0.03).[130] The WHI focused on postmenopausal women.[131] A significant trend was reported between higher 25(OH)D concentrations and lower colorectal cancer risk (OR 2.53, between highest [≥58.4 nmol/L] and lowest quintiles [<31.0 nmol/L]; P for Trend = 0.02).

The Japan PHC compared 25(OH)D concentrations between cases and controls; no significant difference was reported.[128]

Findings per Special Populations

No subgroup data were available regarding the association between 25(OH)D concentrations and colorectal cancer risk in obese persons. **In the original report**, one study exclusively included male smokers aged between 50 and 69 years,[127] and reported no significant association between 25(OH)D concentrations and colorectal cancer risk by trend analysis. Another study that exclusively included white population also found no association.[132] In addition, another study that focused on women who were taking hormone replacement therapy reported no significant association between 25(OH)D and colorectal cancer.[130]

Findings Excluding Early Cases

In the original report, three studies performed sensitivity analyses on the association between 25(OH)D concentrations and colorectal cancer risk by excluding cases diagnosed within the first 1 to 2 years after blood draw.[127,129,130] One study found a significant association between higher 25(OH)D concentrations and lower colon cancer risk (OR 0.3, between highest [>48.2 nmol/L] and lowest quartiles [≤ 24.5 nmol/L]; P for Trend = 0.04), which was not significant in main analysis.[127] Otherwise, the results were not materially different from the main analysis.

Findings on 1,25-Dihydroxyvitamin D

The nested case-control study within the Physicians' Health cohort found no significant associations between 1,25(OH)$_2$D and colorectal, colon, and rectal cancer risk.[126]

In the original report, a total of three studies evaluated the associations between $1,25(OH)_2D$ concentrations and colorectal cancer risk[127,130] or colon cancer.[133] None of the studies found a significant association by trend analysis. One study reported no significant association between $1,25(OH)_2D$ concentrations and rectal cancer risk.[127]

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  Not reviewed
- **19–50 y**
  The analysis of the NHANES III with a mean age of 44 years included participants mostly within this life stage. The study found an inverse association between 25(OH)D and colorectal cancer mortality.
- **51–70 y**
  Three of the nested case-control studies identified for the update report included people with mean age ranged from 59 to 69 years; a fourth study included individuals aged 40–84 (mean age was not reported). A trend between higher 25(OH)D levels and lower risk of colorectal cancer was found in three studies and one study found no association. Of the two studies that also assessed colon and rectal cancer outcomes separately, one study found significant negative trends between 25(OH)D and colon or rectal cancer and one study reported no association.
- **≥71 y**
  In the original report, one RCT with a mean age of 75 included participants mostly within this life stage. The trial found no difference in colorectal cancer mortality or incidence between supplemental vitamin D and no supplements.
- **Postmenopause**
  In the original report, one study and a subgroup analysis in another study focused on postmenopausal women. A trend between higher 25(OH)D concentrations and lower colorectal cancer risk was found in these two studies.
- **Pregnant & lactating women**
  Not reviewed

Table 22. Vitamin D and colorectal cancer: Characteristics of observational studies[A] (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Cohort												
Freedman 2007[103] NHANES III US (various) [16481636]	• Health status • Mean age (range), y • Male (%)	Any 44 (≥17) 45	• Assay method • Season blood drawn	RIA (DiaSorin) All	Colorectal cancer mortality stratified by prespecified baseline 25(OH)D cut points	X	X	X	X	X	X	White: 71%; Black: 14%; Hispanic: 6%; Others: 9%
Nested case-control												
Braun 1995[133] WCC Maryland, US (38°N) [329893]	• Health status • Mean age (range), y • Male (%)	Any 55 (nd) nd	• Assay method • Season blood drawn	RIA (Horris 1993) Fall	• 25(OH)D levels between cases and controls • Colon cancer risk stratified by baseline 25(OH)D quintiles		X			X		
Feskanich 2004[130] NHS US (various) [15342452]	• Health status • Mean age (range), y • Male (%)	Any 60 (43–70) 0	• Assay method • Season blood drawn	RIA (Horris 1997) All	Colorectal cancer risk stratified by baseline 25(OH)D quintiles	X	X	X	X	X	X	Aspirin user (>10 y): 10%; Hormone replacement therapy: 34%
Garland 1989[132] WCC Maryland, US (38°N) [2572900]	• Health status • Mean age (range), y • Male (%)	Any 63 (nd) 50	• Assay method • Season blood drawn	HPLA (Clemens 1982) Fall	• 25(OH)D levels between cases and controls • Colon cancer risk stratified by baseline 25(OH)D quintiles		X			X		White: 100%

Table 22. Vitamin D and colorectal cancer: Characteristics of observational studies[A] (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Cohort												
Otani 2007[128] Japan PHC Japan (various) [17622244]	• Health status • Mean age (range), y • Male (%)	Any Men: 57 (40–69); Women: 56 (40–69)	• Assay method • Season blood drawn	CPBA (Haddad 1971) All	• 25(OH)D levels between cases and controls • Colorectal cancer risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	
Tangrea 1997[127] ATBC Finland (~60°N) [9242478]	• Health status • Mean age (range), y • Male (%)	Smoker[B] 60 (50–69) 100	• Assay method • Season blood drawn	RIA (Horris 1993) All	Colorectal cancer risk stratified by baseline 25(OH)D quartiles	X	X	X		X	X	
Wactawski-Wende 2006[131] WHI US (various) [16481636]	• Health status • Mean age (range), y • Male (%)	Post-menopausal women[C] nd (50–79) 0	• Assay method • Season blood drawn	RIA (DiaSorin) All	Colorectal cancer risk stratified by baseline 25(OH)D quartiles		X	X	X		X	White: 83%; Black: 9%; Hispanic: 4% Others: 4%
Wu 2007[129] HPFS US (various) [17623801]	• Health status • Mean age (range), y • Male (%)	Smoker 5% 66 (nd) 100	• Assay method • Season blood drawn	RIA (Horris 1997) All	• 25(OH)D levels between cases and controls • Colorectal cancer risk stratified by baseline 25(OH)D quintiles	X	X	X	X	X	X	Aspirin user in 1994: 40%; Current smoker: 5%

Table 22. Vitamin D and colorectal cancer: Characteristics of observational studies[A] (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
NEW Nested case-control studies										
Jenab 2010[123] European Prospective Investigation into Cancer and Nutrition (EPIC) Multiple Countries	• Health status nd • Mean age (SD), y 58.6 (SD 7.2) • Male (%) 49.7%		• Colorectal cancer risk stratified by baseline 25(OH)D quintiles • Rectum cancer stratified by baseline 25(OH)D quintiles	X	X	X		X	X	age, % female is of controls-colon cancer
Lee, 2011[126] Physicians US (various cities)	• Health status Healthy • Mean age (SD), y nd (nd) • Male (%) 100		• Colorectal cancer risk stratified by baseline 25(OH)D quartiles • Colon cancer stratified by baseline 25(OH)D quartiles	X	X	X		X	X	
Neuhouser, 2012[124] WHI US (various cities)	• Health status Post-menopausal • Mean age (SD), y 65.1 (SD 6.8) • Male (%) 0%		Colorectal cancer risk stratified by baseline 25(OH)D quartiles	X	X	X			X	two nested case controls: this one represents the CRC dataset and the one we renumber represents the breast cancer dataset
Woolcott, 2010[125] Multiethnic Cohort Study US, Hawaii/Los Angeles	• Health status nd • Mean age (SD), y 69.2 (SD 7.9) • Male (%) nd		Colorectal cancer risk stratified by baseline 25(OH)D sextiles		X	X				

Table 22. Vitamin D and colorectal cancer: Characteristics of observational studies[A] (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
NEW Cohort study										
Ordonez-Mena 2013[97] ESTHER Saarland, Germany	• Health status • Mean age (SD), y • Male (%)	Nd NR (50–74) 54%	Colorectal cancer stratified by baseline 25(OH)D tertiles	X	X	X			X	confounders-add multivitamin use, fish consumption, red meat consumption, daily fruit intake, daily vegetable intake, scholarly education, physical activity, family history of cancer

[A]This table is ordered alphabetically by study author.
[B]Participants of a lung cancer prevention 2 by 2 RCT of alpha-tocopherol and beta-carotene.
[C]Participants of a hip fracture prevention RCT of vitamin D3 and calcium.

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Cohort study										
Colorectal cancer mortality										
Women										
Freedman 2007[103]	19–50[A]	Colorectal Cancer Mortality (66/16818; 0.004)	nd	<50	28	~5606	**1**	**Reference**	0.02	B
	51–70			50–80	24	~5606	0.44	0.20, 0.95*		
[17971526]	≥71			≥80	14	~5606	0.28	0.11, 0.68*		
Nested case-control study										
Colorectal cancer										
Men										
Otani 2007[128] Japan PHC	19–50	Colorectal cancer (N=196 cases; 392 controls)	1–13	<57.2	43	74	**1**	**Reference**	0.39	B
	51–70[A]			57.2–69.0	40	85	0.76	0.42, 1.4		
[17622244]				69.0–80.2	36	85	0.76	0.39, 1.5		
				≥80.2	44	80	0.73	0.35, 1.5		
Wu 2007[129]	19–50	Colorectal cancer (179 cases; 356 controls)	1–9	46, median	45	71	**1**	**Reference**	0.24[B]	
HPFS	51–70[A]			62.5	44	71	0.97	0.55, 1.70		B
[17623801]	≥71			72.8	30	68	0.66	0.35, 1.24		
				83.3	23	74	0.51	0.27, 0.97*		
				98.5	37	72	0.83	0.45, 1.52		
	19–50	Colorectal cancer, age <65		48.2, median	25	34	**1**	**Reference**	0.13	
	51–70[A]			66.8	15	28	1.03	0.36, 2.91		
				80	9	30	0.38	0.12, 1.26		
				97	14	36	0.45	0.15, 1.40		
	51–70[A]	Colorectal cancer, age ≥65		48.2, median	34	55	**1**	**Reference**	0.34	
	≥71			66.8	36	61	0.97	0.50, 1.87		
				80	19	58	0.56	0.27, 1.15		
				97	27	54	0.83	0.39, 1.75		

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Tangrea 1997[127] ATBC [9242478]	19–50 51–70[A]	Colorectal cancer (146 cases; 292 controls)	1–8	≤24.5	46	72	**1**	**Reference**	0.13	B
				24.5–34.7	35	73	0.7	0.4, 1.3		
				34.7–48.2	36	73	0.8	0.4, 1.3		
				>48.2	29	72	0.6	0.3, 1.1		
Women										
Wactawski-Wende 2006[131] WHI [16481636]	Post-menopausal women	Colorectal cancer (306 cases; 306 controls)	1–12	<31.0	88	67	2.53	1.49, 4.32	0.02	B
				31.0–42.3	80	73	1.96	1.18, 3.24*		
				42.4–58.3	78	73	1.95	1.18, 3.24*		
				≥58.4	60	93	**1**	**Reference**		
Feskanich 2004[130] NHS [15342452]	19–50 51–70[A]	Colorectal cancer (192 cases; 384 controls)	1–11	40.2, median	53	77	**1**	**Reference**	0.02[C]	B
				55.1	47	79	0.93	0.53, 1.63		
				66.7	35	75	0.79	0.44, 1.40		
				77.5	29	77	0.58	0.31, 1.07		
				99.1	29	75	0.53	0.27, 1.04		
Otani 2007[128] Japan PHC [17622244]	19–50 51–70[A]	Colorectal cancer (179 cases; 358 controls)	1–13	<57.2	41	77	**1**	**Reference**	0.74	B
				57.2–69.0	34	73	1	0.55, 1.9		
				69.0–80.2	44	71	1.2	0.65, 2.3		
				≥80.2	41	76	1.1	0.50, 2.3		
Colon cancer										
Both sexes										
Braun 1995[133] WCC [329893]	19–50 51–70[A] ≥71	Colon cancer (57 cases; 114 controls)	1–17	<43	nd	nd	**1**	**Reference**	0.57	C
				43.0–51.5	nd	nd	0.3	0.1, 1.0		
				51.5–61.8	nd	nd	0.5	0.2, 1.5		
				61.8–75.3	nd	nd	0.7	0.2, 2.0		
				≥75.3	nd	nd	0.4	0.1, 1.4		

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Garland 1989[132] WCC [2572900]	19–50	Colon cancer (34 cases; 67 controls)	1–9	10 to <50	9	8	**1**	**Reference**		
	51–70[A]			50.0–67.5	7	13	0.48	0.13, 1.80	0.41	C
	≥71			67.5–82.5	5	18	0.25	0.06, 0.98*		
				82.5–105	4	17	0.21	0.05, 0.89*		
				105–227.5	9	11	0.73	0.20, 2.66		
Men										
Otani 2007[128] Japan PHC [17622244]	19–50	Colon cancer (141 cases; 282 controls)	1–13	<57.2	25	54	**1**	**Reference**		
	51–70[A]			57.2–69.0	27	55	0.98	0.48, 2.0	0.7	B
				69.0–80.2	29	66	1	0.48, 2.3		
				≥80.2	38	62	1.2	0.51, 2.7		
Wu 2007[129] HPFS [17623801]	19–50	Colon cancer (139 cases; 276 controls)	1–9	48.3, median	49	66	**1**	**Reference**		
	51–70[A]			66.8	44	68	0.74	0.42, 1.33	0.005[D]	B
	≥71			80	17	68	0.29	0.14, 0.59*		
				97	29	74	0.46	0.24, 0.89*		
Tangrea 1997[127] ATBC [9242478]	19–50	Colon cancer (91 cases; 182 controls)	1–8	≤24.5	30	47	**1**	**Reference**		
	51–70[A]			24.5–34.7	18	47	0.6	0.3, 1.2	0.69[E]	B
				34.7–48.2	22	45	0.8	0.4, 1.6		
				>48.2	21	42	0.8	0.4, 1.6		
Women										
Feskanich 2004[130] NHS [15342452]	19–50	Colon cancer (148 cases; 296 controls)	1–11	41.2, median	41.2	75	**1**	**Reference**		
	51–70[A]			59.7	59.7	71	1.03	0.56, 1.89	0.17	B
				73.3	73.3	77	0.54	0.28, 1.03		
				98.1	98.1	72	0.7	0.35, 1.38		

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Otani 2007[128] Japan PHC [17622244]	19–50	Colon cancer (115 cases; 230 controls)	1–13	<57.2	21	53	**1**	**Reference**	0.12	B
	51–70[A]			57.2–69.0	27	48	1.7	0.78, 3.6		
				69.0–80.2	27	41	2.1	0.90, 4.7		
				≥80.2	31	53	2.1	0.78, 5.6		
Rectal cancer										
Men										
Otani 2007[128] Japan PHC [17622244]	19–50	Rectal cancer (55 cases; 110 controls)	1–13	<57.2	18	20	**1**	**Reference**	0.06	B
	51–70[A]			57.2–69.0	13	30	0.17	0.02, 1.2		
				69.0–80.2	7	19	0.25	0.05, 1.3		
				≥80.2	6	18	0.075	0.005, 0.99		
Tangrea 1997[127] ATBC [9242478]	19–50	Rectal cancer (55 cases; 110 controls)	1–8	≤24.5	16	25	**1**	**Reference**	0.06[F]	B
	51–70[A]			24.5–34.7	17	26	0.9	0.4, 2.4		
				34.7–48.2	14	28	0.8	0.3, 2.0		
				>48.2	8	30	0.4	0.1, 1.1		
Wu 2007[129] HPFS [17623801]	19–50	Rectal cancer (40 cases; 80 controls)	1–9	53.0, median	11	30	**1**	**Reference**	0.08	B
	51–70[A]			73.3	15	28	1.74	0.61, 5.00		
	≥71			93.5	14	22	3.32	0.87, 12.69		
Women										
Otani 2007[128] Japan PHC [17622244]	19–50	Rectal cancer (64 cases; 128 controls)	1–13	<57.2	20	24	**1**	**Reference**	0.17	B
	51–70[A]			57.2–69.0	7	25	0.26	0.07, 1.0		
				69.0–80.2	17	30	0.46	0.15, 14		
				≥80.2	10	23	0.33	0.08, 1.3		
Feskanich 2004[130] NHS [15342452]	19–50	Rectal cancer (44 cases; 88 controls)	1–11	44.4, median	24	31	**1**	**Reference**	0.03	B
	51–70[A]			66.2	10	26	92.4	10 0.8, 1.31		

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
NEW Nested case-control studies										
Colorectal cancer										
Jenab 2010[123] European Prospective Investigation into Cancer and Nutrition (EPIC)	30–77 years	Colorectal Cancer (1248 cases;1248 controls)	NR	Quintile 1:<25	64	116	RR=1.32	0.87, 2.01		
				Quintile 2:25–50	473	873	1.28	1.05, 1.56		
				Quintile 3:50–75	448	909	1	**Reference**		
				Quintile 4:75–100	173	382	0.88	0.68, 1.13		
				Quintile 5:>100	90	216	0.77	0.56, 1.06	<0.001	B
Lee 2011[126] Physicians Health Study	40–84 years	Colorectal Cancer (229 cases;389 controls)	NR	Quartile 1 (median39.3 nmol/L)	57	153	1.00	**Reference**		
				Quartile 2 (median 55.8 nmol/L)	41	138	0.71	0.42, 1.21		
				Quartile 3(median 66.8 nmol/L)	74	173	1.24	0.76, 2.04		
				Quartile 4(median 94.75 nmol/L	57	154	1.08	0.62, 1.87	0.67	B
Neuhouser 2012[124] WHI	50–79 years	Colorectal Cancer (1080 cases;1080 controls)	NR	<32.7	293	562	4.45	1.96, 10.10		
				32.7–43.6	306	578	2.76	0.72, 3.14		
				43.6–64.5	250	520	1.51	1.30, 5.89		A
				>64.5	231	500	1.00	**Reference**	0.003	
Woolcott 2010[125] multiethnic cohort	45–75 years	Colorectal Cancer (229 casea;434 controls)	NR	<42 nmol/L	67	154	1.00	**Reference**		
				42.0–55.5 nmol/L	42	128	0.63	0.37, 1.08		
				55.5–65.8 nmol/L	38	126	0.54	0.32, 0.93		A
				65.8–82.0 nmol/L	43	130	0.62	0.36, 1.07		
				≥82.0 nmol/L	39	125	0.60	0.33, 1.07		
				Per doubling	NR	NR	0.68	0.51, 0.92	0.010	

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Colon cancer										
Lee 2011[126] Physicians Health Study	40–84 years	Colon Cancer (136 casesa;287 controls)	NR	Quartile 1 (median 39.25 nmol/L)	36	106	1.00	**Reference**		B
				Quartile 2 (median 55.75 nmol/L)	37	109	0.95	0.52, 1.74		
				Quartile 3 (median 66.8 nmol/L)	52	126	1.34	0.75, 2.39		
				Quartile 4 (median 94.75 nmol/L)	47	118	1.38	0.73, 2.64	0.350	
Jenab 2010[123] European Prospective Investigation into Cancer and Nutrition (EPIC)	30–77 years	Colon Cancer (785 cases;785 controls)	NR	<25nmol/l	45	72	1.90	1.10, 3.29		B
				≥25<50nmol/l	300	549	1.36	1.05,1.76		
				≥50<75nmol/l	286	581	1	**Reference**		
				≥75<100nmol/l	104	242	0.86	0.62, 1.17		
				≥100nmol/l	50	126	0.71	0.46, 1.08	<0.001	
Rectal cancer										
Jenab 2010[123] European Prospective Investigation into Cancer and Nutrition (EPIC)	30–77 years	Rectal Cancer (463 cases, 463 controls)	NR	<25nmol/l	NR	NR	0.77	0.37, 1.59		B
				≥25<50nmol/l	NR	NR	1.17	0.84, 1.65		
				≥50<75nmol/l	NR	NR	1.00	**Reference**		
				≥75<100nmol/l	NR	NR	0.93	0.60, 1.45		
				≥100nmol/l	NR	NR	0.82	0.48, 1.40	0.320	
Lee 2011[126] Physicians Health Study	40–84 years	Rectal Cancer (57 cases, 102 controls)	NR	Quartile 1 (median 39.3 nmol/L)	20	44	1.00	**Reference**		B
				Quartile 2 (median 55.8 nmol/L)	15	41	0.53	0.18, 1.60		
				Quartile 3 (median 66.8 nmol/L)	9	37	0.42	0.13, 1.40		
				Quartile 4 (median 94.8 nmol/L)	13	37	0.45	0.14, 1.46	0.050	

Table 23. Vitamin D and colorectal cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Colon cancer										
NEW Cohort study										
Ordonez-Mena 2013[97] ESTHER		Colorectal Cancer	8 yrs	Q1	37	2373	HR 1.02	0.68, 1.53		B
				Q2+Q3	69	4741	HR 1.00	**Reference**		
				Q4	30	2368	HR 0.77	0.50, 1.20		

* Statistically significant (P<0.05).
[A]Most representative life stage.
[B]P for trend = 0.31 when cases diagnosed within 2 years of blood collection were excluded.
[C]Results were not notably changed when cases diagnosed within the first year after blood collection were excluded (P for trend not reported). Subgroup analyses per age were also reported as follows: Age ≥ 60, OR = 0.35 (95% CI 0.14, 0.87) between the lowest and highest quintiles; P for trend = 0.006. Age < 60, OR = 1.36 (95% CI 0.48, 3.92) between the lowest and highest quintiles; P for trend = 0.70.
[D]P for trend = 0.008 when cases diagnosed within 2 years of blood collection were excluded.
[E]P for trend = 0.58 when cases diagnosed within 2 years of blood collection were excluded.
[F]P for trend = 0.04 when cases diagnosed within 2 years of blood collection were excluded.

Figure 8. Colorectal cancer risk stratified by vitamin D concentration

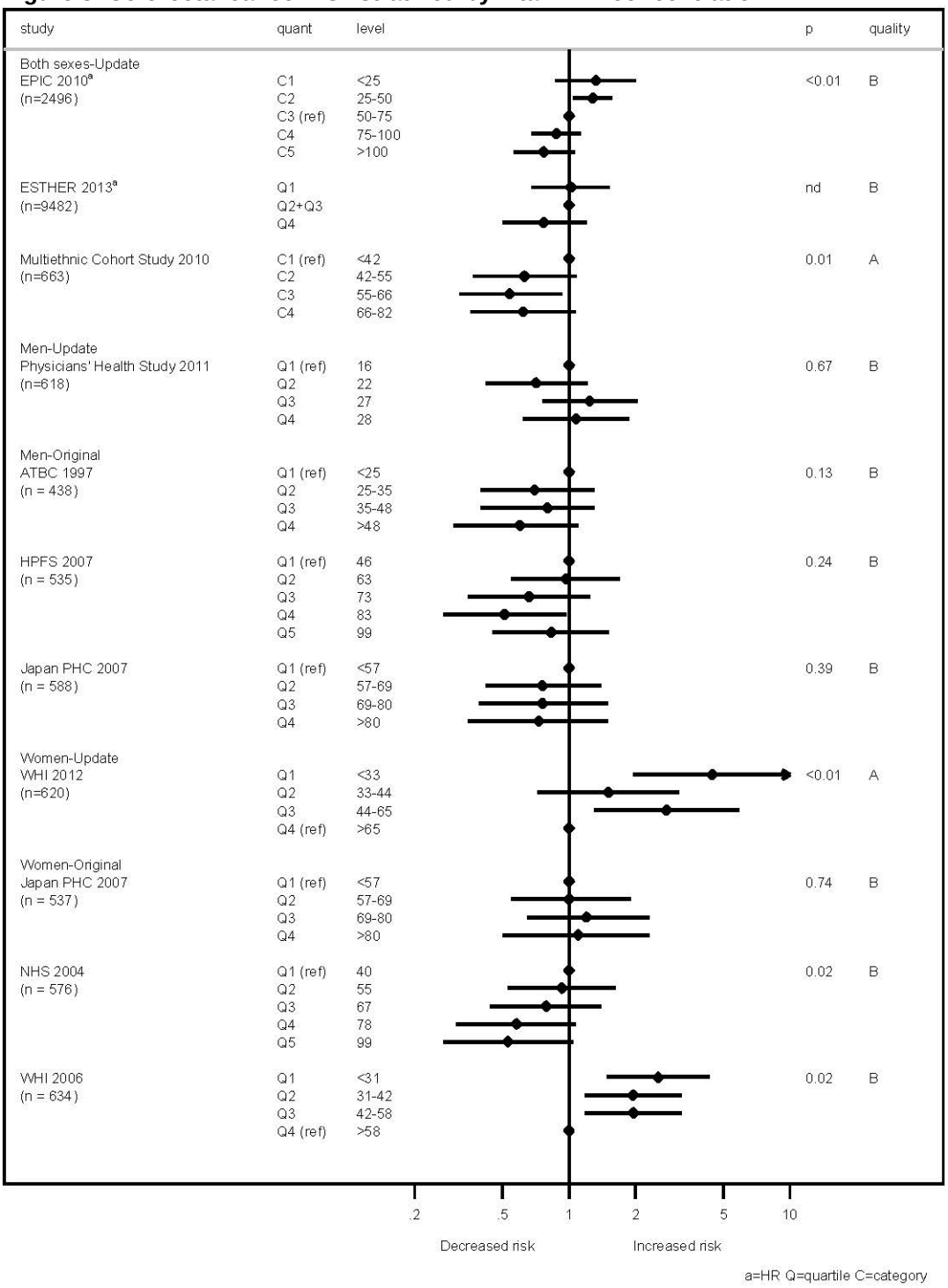
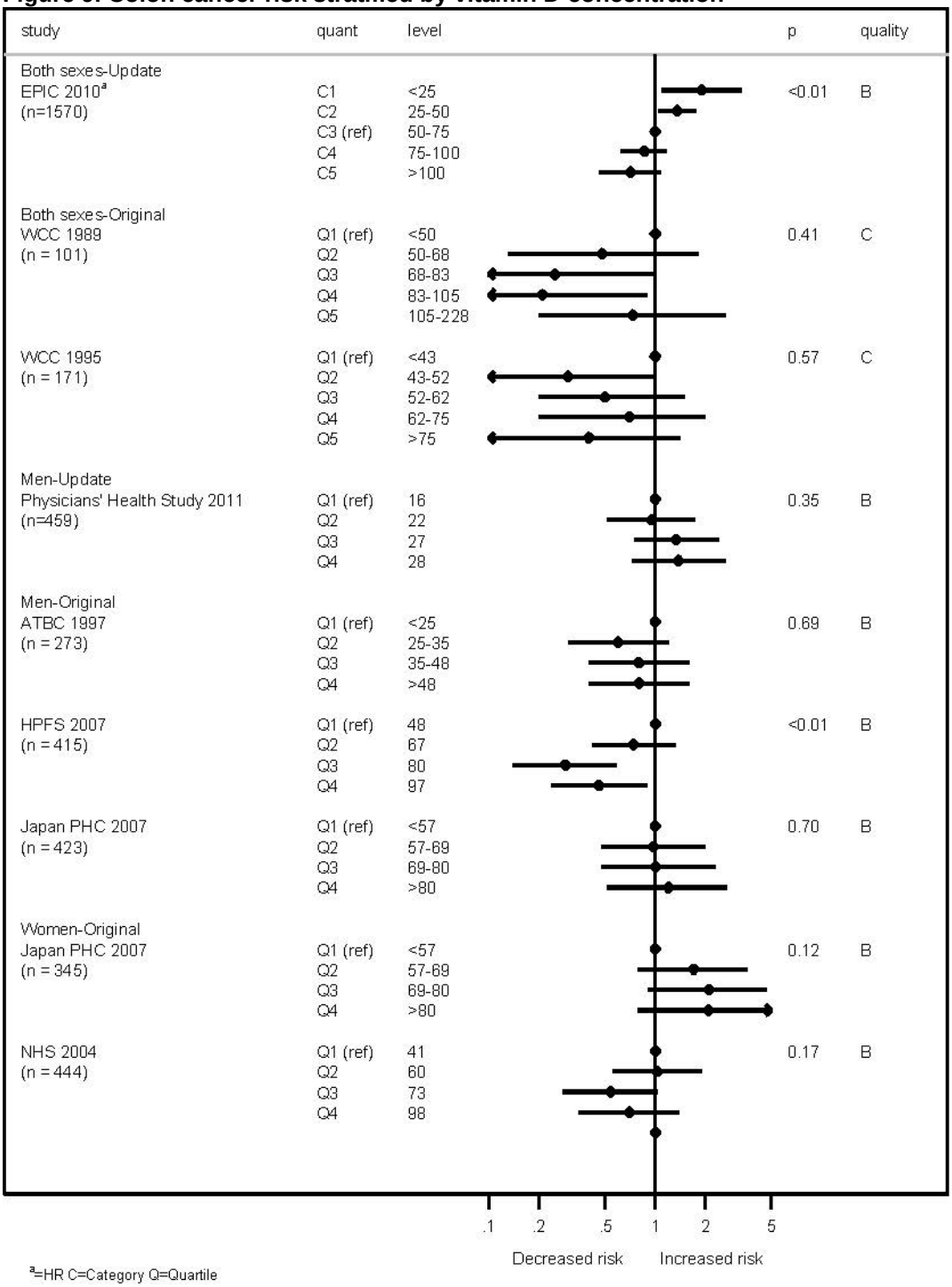
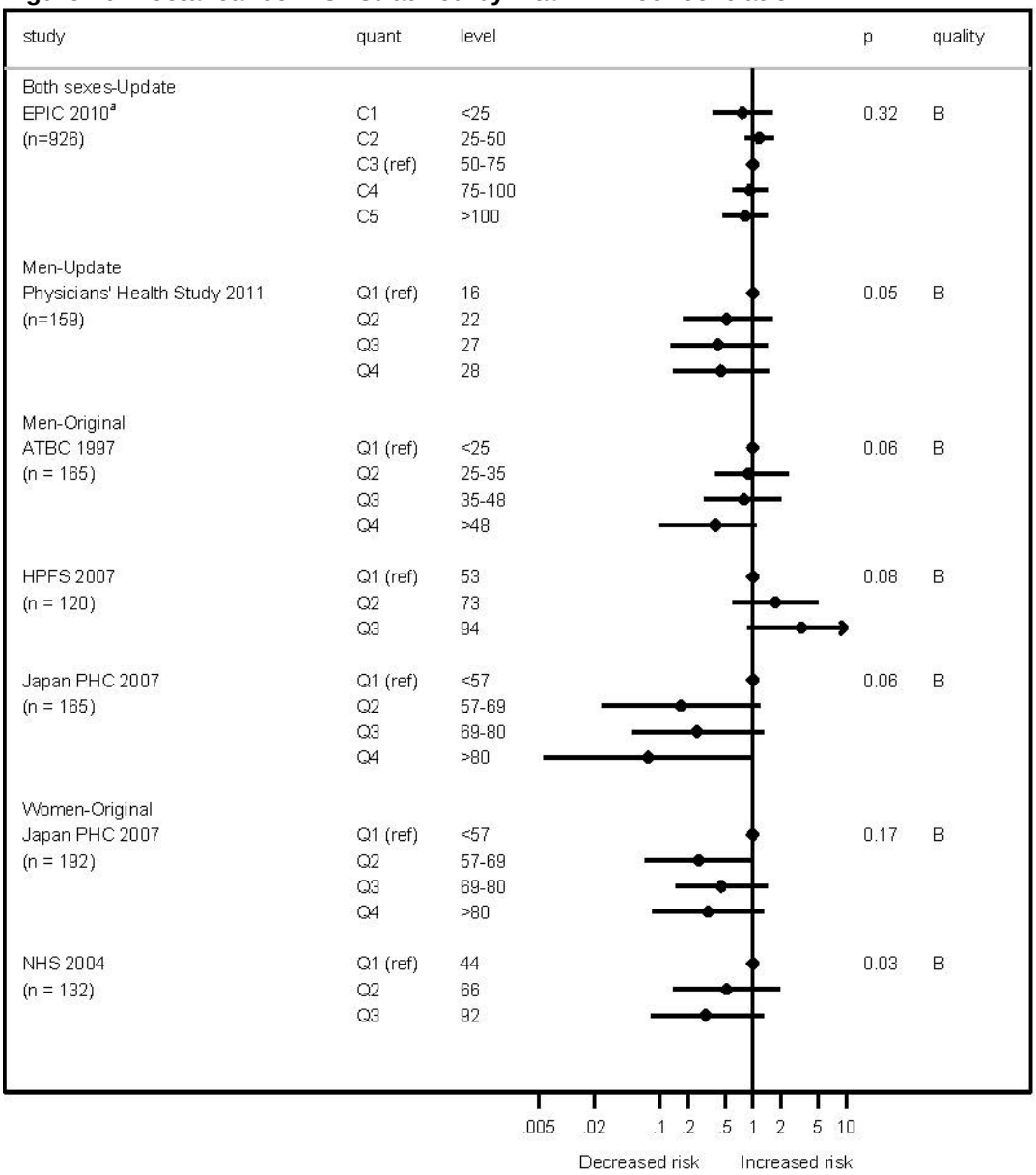


Figure 9. Colon cancer risk stratified by vitamin D concentration



[a]=HR C=Category Q=Quartile

Figure 10. Rectal cancer risk stratified by vitamin D concentration



[a]=HR C=Category Q=Quartile

Colorectal Adenoma

Synopsis

No **qualified** systematic reviews have evaluated the association between 25(OH)D concentrations and the risk of colorectal adenoma. **No new studies were identified for the update report. In the original report**, one B quality nested case-control study in women found no significant association between 25(OH)D concentrations and the risk of colorectal adenoma.

Detailed Presentation (Tables 24 & 25)

In the original report, one nested case-control study within the NHS evaluated the relationship between 25(OH)D concentrations and the risk of colorectal adenoma in women.[134] At 5 years, an adjusted analysis found no significant association between 25(OH)D concentrations and the incidence of colorectal adenoma by trend analysis. Subgroup analyses also found no significant association between 25(OH)D concentrations and the incidence of colon or rectal adenoma. No subgroup data were available regarding age or other special populations (e.g., obese, smokers, ethnic groups, or users of contraceptives). This study was rated B because it excluded more than 50 percent of participants of the original cohort because their blood samples were not available.

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  Not reviewed
- **19–50 y**
  A proportion of participants in the NHS was in this life stage. No unique conclusions are possible for this life stage separate from those for people 51 to 70 years.
- **51–70 y**
  The analysis of the NHS included female participants mostly within this life stage. The study found no association between 25(OH)D and the incidence of colorectal adenoma.
- **≥71 y**
  A proportion of participants in the NHS was in this life stage. No unique conclusions are possible for this life stage separate from those for people 51 to 70 years.
- **Postmenopause**
  The analysis of NHS partially included postmenopausal women. However, no unique conclusions are possible for this life stage separate from those for people 51 to 70 years.
- **Pregnant & lactating women**
  Not reviewed

Table 24. Vitamin D and colorectal adenoma: Characteristics of observational studies [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Nested Case-Control												
Platz 2000[134] NHS US (various) [11045788]	• Health status • Mean age (SD), y • Male (%)	Any 59 (7) 0	• Assay method • Season blood drawn	RIA (Horris 1993) All	• Colorectal adenoma risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	Aspirin user: 26%; Hormone replacement therapy: 36%

Table 25. Vitamin D and colorectal adenoma: Results of observational studies [no new studies in the current report]

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Nested case-control study										
Colorectal adenoma										
Women										
Platz 2000[134] NHS [11045788]	19–50	Colorectal adenoma (326 cases; 326 controls)	5	16.3, median	103	82	**1**	**Reference**	1.0	B
	51–70[A]			22.6	62	80	0.64	0.41, 1.00		
				28.3	61	82	0.58	0.36, 0.95		
	≥71			38.0	100	82	1.04	0.66, 1.66		
Colon adenoma										
Women										
Platz 2000[134] NHS [11045788]	19–50	Colon adenoma (261 cases; 261 controls)	5	16.3, median	79	64	**1**	**Reference**	1.0	B
	51–70[A]			22.6	55	64	0.71	0.43, 1.18		
				28.3	51	69	0.60	0.35, 1.02		
	≥71			38.0	76	64	1.02	0.60, 1.73		
Rectal adenoma										
Women										
Platz 2000[134] NHS [11045788]	19–50	Rectal adenoma (65 cases; 65 controls)	5	16.3, median	24	18	**1**	**Reference**	0.9	B
	51–70[A]			22.6	7	16	0.38	0.12, 0.19		
				28.3	10	13	0.34	0.08, 1.42		
	≥71			38.0	24	18	1.59	0.50, 5.03		

* Statistically significant (P<0.05)
[A]Most representative life stage

Breast Cancer

Synopsis

No qualified systematic reviews evaluated the association between vitamin D and calcium intake or serum 25(OH)D concentration and risk of breast cancer. **One cohort study compared serum 25(OH)D and the risk of breast cancer-specific mortality and found no association. Eight observational studies that assessed the association between 25(OH)D and breast cancer were identified for the current report. Two cohort and four nested case-control studies found no association.[124,135-137] Two nested case-control studies found increasing risk of breast cancer with decreasing 25(OH) concentrations.[138,139]**

Two studies that examined the relationship between vitamin D and calcium intake or 25(OH)D and breast density were identified. A RCT found a decrease in percent mammographic density among women who had ≥400 IU/d total vitamin D intake.[140] A nested case-control found lower risk of increased mammographic density with 25(OH) concentrations above the first quartile.[141]

In the original report, one cohort study compared serum 25(OH)D concentrations and the risk of breast cancer-specific mortality,[103] and two nested case-control studies compared 25(OH)D concentrations and the risk of breast cancer.[142,143] The cohort study utilizing NHANES III data found significant decrease in breast cancer-specific mortality during 9 years of follow up in those with serum concentration of 25(OH)D greater than 62 nmol/L. The Nurses' Health Study and Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, however, found no significant relationship between serum concentration of 25(OH) D and risk of breast cancer diagnosis in either pre- or postmenopausal women during 7 to 12 years of follow up.[142,143] All three studies were rated B quality.

Detailed Presentation (Tables 26a-d & 27a-d)

Nine observational studies that assessed the association between 25(OH)D and breast cancer incidence were identified for the current report. One observational study that assessed the association between 25(OH)D and breast cancer-specific mortality was also identified.

Two cohort studies, within the Women's Healthy Eating and Living (WHEL) Study and the Nurses' Health Study II (NHSII) and the ESTHER study, found no association between 25(OH)D and breast cancer (all rated B).[97,144]The study in the WHEL cohort also found no association after stratifying by pre- and post-menopause. The Health, Eating, Activity, and Lifestyle (HEAL) cohort study found no association between 25(OH)D and breast cancer-specific mortality (rated B).

Six nested case-control studies were identified. Four of the nested case-control studies found no association between 25(OH)D concentrations and breast cancer incidence (rated 3A, 1B).[124,136,137] The other two nested case-control studies found increasing risk of breast cancer with decreasing 25(OH) concentrations (both rated B).[138,139] In one of these, a stratified analysis by menopause status found the negative trend remained for premenopausal women but not for postmenopausal women.[139]

Two studies with breast density outcomes were identified. The Women's Health Initiative (WHI) Mammogram Density Ancillary Study found a decrease in percent mammographic density among women who had ≥400 IU/d total vitamin D intake and were

enrolled in the vitamin D_3 400 IU + 1,000 mg calcium per day arm of the trial.[140] A nested case-control study within the Nurses' Health Study found lower percent mammographic density in women who had 25(OH)D levels above the first quartile; statistical significance was not assessed.[141]

From the original report, the NHANES III study followed 16,818 adults with a mean age of 44 years with a background calcium intake on average of about 812 mg/day (from diet and supplements).[103] The study included 71% non-Hispanic white, 14% non-Hispanic black, 6% Mexican American, and 9% from other races. During 9 years of follow up, women with serum concentration of 25(OH) D greater than 62 nmol/L had a hazard ratio of 0.28 for breast cancer-specific mortality compared to those with 62 nmol/L or lower (95% CI 0.08–0.93). The breast cancer-specific mortality was one of many cancer-specific mortality outcomes reported in this study.

In the original report, two nested case-control studies of women with a mean age of 57 years and 67 years, respectively, found no relationship between serum 25(OH)D concentrations and risk of breast cancer.[142,143] However, in the second study, when compared with the lowest quintile, quintiles 3 to 5 were associated with nonsignificantly elevated risks. In multivariable adjusted analyses, the risk associated with 25(OH)D levels below 37.5 nmol/L compared with higher levels was 0.81 (95% CI 0.59, 1.12).[143]

Findings by Age and Sex

In the original report, in the one nested case-control study (methodological quality B) including both premenopausal and postmenopausal women, no relationship was found between serum 25(OH)D levels and risk of breast cancer. However, in this study, there was a statistically significant trend towards decreased risk of breast cancer among women older than 60 years of age with serum concentration of 25(OH)D greater than 62 nmol/L.

Findings by Life Stage

- **0–6 mo**
  Not applicable
- **7 mo–2 y**
  Not applicable
- **3–8 y**
  Not applicable
- **9–18 y**
  Not applicable
- **19–50 y**
  In the NHSII cohort study, 25(OH)D concentration from women aged 32–54 years was not associated with breast cancer incidence. In the original report, a follow up study of NHANES III including women with a mean age of 44 years found a decreased mortality (hazard ratio 0.28) due to breast cancer among those with serum concentration of 25(OH)D greater than 62 nmol/L.
- **51–70 y**
  The ESTHER study found no association between serum 25(OH)D concentration and breast cancer incidence in women aged 50–74 years. The WHI Mammogram Density Ancillary Study found an association between vitamin D intake and percent mammographic density in women aged 50 to 79 who had ≥400 IU/d total vitamin D

intake.[140] The nested case-control studies identified for the update report included individuals with mean age ranged from 57 to 65 years. A trend between higher 25(OH)D levels and lower risk of breast cancer was found in two studies; the other two studies found no association. In the original report, two nested case-control studies of women with a mean age of 57 years and 67 years, respectively, found no relationship between vitamin D levels and risk of breast cancer. However, in one of these studies, there was a statistically significant trend towards decreased risk of breast cancer among women older than 60 years of age with serum concentration of 25(OH)D greater than 62 nmol/L.

- **≥71 y**
  Not reviewed
- **Postmenopause**
  In the WHEL cohort study, no significant trends were found between 25(OH)D and breast cancer in pre- and post-menopausal women.[144] In a nested case-control study, no association was found between breast cancer risk and 25(OH)D in postmenopausal women.[139]
- **Pregnant & lactating women**
  Not reviewed

Table 26a. Vitamin D and breast cancer: Characteristics of nested case-control studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
							Demograph		Medical		Lifestyle	
Nested Case-Control												
Bertone-Johnson 2005[142] NHS US (38º N) [16103450]	• Health status • Mean age (range/SD), y	No Cancer 57 (7.0)	• Assay method • Season blood drawn	RIA All year	Breast cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5		X		X		X	
Freedman 2008[143] PLCO Trial US (38º N) [18381472]	• Health status • Mean age (range/SD), y	No Cancer 67 (ND)	• Assay method • Season blood drawn	RIA Dec-Sep	Breast cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5		X		X		X	
NEW Studies												
Nested Case-Control												
Neuhouser 2012[124] WHI US (various)	• Health status • Mean age (SD), y	Post-menopausal 65.1 (SD 6.8)					X				X	two nested case controls: this one represents the CRC dataset and the one we renumber represents the breast cancer dataset

Table 26a. Vitamin D and breast cancer: Characteristics of nested case-control studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Nested Case-Control											
Almquist, 2010[137] Malmo Diet and Cancer Study	• Health outcome • Mean age (SD), y	Healthy 57 (SD 7.3)		Breast cancer risks: Quartile 1 vs. Quartile 2, 3, 4							
Engel, 2010[138] French E3N France	• Health outcome • Mean age (SD), y	nd 56.9 (6.4)		Breast cancer risks: Quintile 1 vs. Quintile 2, 3		X	X				
McCullough, 2009[136] Cancer Prevention Study-II (CPS-II)	• Health outcome • Mean age (SD), y	nd 69.6 (5.8)		Breast cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5		X	X		X		
Rejnmark, 2009[139] Denmark	• Health outcome • Mean age (SD), y	nd 58 (29–87)		Breast cancer risks: Tertile 1 vs. Tertile 2, 3							
NEW Cohort study											
Kuhn 2013[145] EPIC Multiple Countries	• Health outcome • Mean age (SD), y	Nd 50.7 (SD 8.8)		Breast Cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5		X	X		X	X	This analysis does not include data from the Malmo site, as these data were analyzed and published separately as Almquist, 2010, reference 126 in the original report.

Table 26b. Vitamin D and breast cancer: Characteristics of prospective cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Freedman 2007[103] NHANES III US (38º N) [17971526]	• Health status • Mean age (range/SD), y	Non-institutionalized 44 (ND)		Breast cancer risks: Quintile 1 vs. Quintile 2	X	X	X		X	X	
NEW Studies											
Jacobs, 2011[144] Women's Healthy Eating and Living (WHEL) US (various)	• Health outcome • Mean age (SD), y • Male (%)	Cancer in remission 51.9 (SD 9) 0%		Breast cancer risks: Quartile 4 vs. Quartile 1, 2, 3							This article contains both prospective cohort and case-control data. Case-control data given here
Eliassen, 2011[135] NHSIII	• Health outcome • Mean age (SD), y • Male (%)	nd 44.9 (SD 4.4) 0%		Breast cancer risks: Quartile 1 vs. Quartile 2, 3, 4							
NEW Cohort study											
Ordonez-Mena 2013[97] ESTHER Saarland, Germany	• Health status • Mean age (range/SD), y • Male (%)	nd NR (50–74) 54%		Breast cancer risk: Tertile 2 vs. Tertile 1 and 3		X	X			X	confounders-add multivitamin use, fish consumption, red meat consumption, daily fruit intake, daily vegetable intake, scholarly education, physical activity, family history of cancer

Table 26c. Vitamin D and breast density: Characteristics of RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
New Studies											
Bertone-Johnson, 2012[140] WHI Mammogram Density/Ancillary Study US	• Health outcome • Mean age (SD), y • Male (%)	Post-menopausal 62 (SD 8) 0%		Percent mammographic density stratified by 25(OH)D_3 medians							

Table 26d Vitamin D and breast density: Characteristics of nested case-control studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
New Studies											
Green 2010[141] Nurses' Health Study US (various)	• Health outcome • Mean age (SD), y • Male (%)	Post-menopausal 61 (nd) 0%		Percent mammographic density stratified by 25(OH)D_3 quartiles							

Table 27a. Vitamin D and breast cancer: Results of nested case-control studies (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Bertone-Johnson 2005[142] NHS [16103450]	Pre- and Post-menopausal	Breast cancer (701/1425)	<1–82 mo	25(OH)D	≤50 (1st batch)	159	297	**1**	**Reference**	nd	B
					≤70 (2nd batch)						
					≤45 (3rd batch)						
					51–70	149	278	0.95	0.66, 1.36		
					72–85						
					47 to 60						
					72–82	125	266	0.74	0.51, 1.06		
					87–97						
					62–72						
					85–97	144	296	0.8	0.58, 1.11		
					100–117						
					75–90						
					≥100	124	265	0.73	0.49, 1.07		
					≥120						
					≥92						
		Breast cancer <60 y (701/1425)				97	191	**1**	**Reference**	NS	
						84	170	0.96	0.62, 1.49		
						77	164	0.8	0.51, 1.26		
						90	192	0.85	0.55, 1.32		
						70	146	0.92	0.57, 1.48		

Table 27a. Vitamin D and breast cancer: Results of nested case-control studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Freedman 2008[143] PLCO Cancer Screening Trial [18381472]	Pre- and Post-menopausal	Breast cancer ≥60 y (701/1425)	12 y	25(OH)D		62	109	**1**	**Reference**	**0.03**	B
						65	114	1.07	0.60, 1.92		
						48	105	0.64	0.35, 1.16		
						54	99	0.68	0.38, 1.24		
						54	125	0.57	0.31, 1.04		
		Breast cancer (1005/2010)			<46	172	2010	**1**	**Reference**	NS	
					46–58	188	2010	1.02	0.75, 1.41		
					59–71	244	2010	1.36	0.99, 1.87		
					72–83	205	2010	1.13	0.82, 1.55		
					≥84	196	2010	1.04	0.75, 1.45		
NEW Studies											
Neuhouser 2012[124] WHI	50–79 years	Breast Cancer (1080 cases, 1080 controls)	NR	25(OH)D	<36.7	105	181	1.06	0.78, 1.43	0.60	A
					36.7 to <50.9	68	147	1.11	0.83, 1.49		
					50.9 to <64.9	84	162	0.99	0.75, 1.31		
					>64.9	53	130	1.00	**Reference**		
Almquist 2010[137] Malmo Diet and Cancer Study	Born 1923–1950	Breast Cancer (213 cases, 213 controls)	7.0 years	25(OH)D3	Quartile 1(<70l)	NR	213	OR=1.00	**Reference**		A
					Quartile 2 (71–86)	NR	164	0.84	0.60,1.15		
					Quartile 3(87–105)	NR	176	0.84	0.60, 1.17		
					Quartile 4(>105)	NR	192	0.93	0.66,1.33	0.71	
			7.0 years	25(OH)D2+D3	Quartile 1(72)	NR	191	1.00	**Reference**		
					Quartile 2 (72–87)	NR	170	0.95	0.68, 1.31		
					Quartile 3(88–106)	NR	183	0.94	0.68, 1.32		
					Quartile 4(>106)	NR	191	0.96	0.68, 1.37	0.78	
Engel 2010[138] French E3N	born between 1925 and 1950	Breast Cancer (636 cases, 1272 controls)	≤10 years	25(OH)D	<49.5 nmol/L	226	630	OR=1.00	**Reference**		A
					49.5–67.5 nmol/L	198	600	0.81	0.63, 1.04		
					>67.5 nmol/L	191	603	0.73	0.55, 0.96	0.02	

Table 27a. Vitamin D and breast cancer: Results of nested case-control studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
McCullough 2009[136] Cancer Prevention Study-II (CPS-II)	47–85 years	Breast Cancer(516 cases, 516 controls)	1month–6.9 years	25(OH)D	<36.7	89	193	OR=1.00	**Reference**		A
					36.7–49.7	115	217	1.29	0.86, 1.94		
					49.8–60.7	99	204	1.14	0.75, 1.72		
					60.8–73.1	118	220	1.44	0.96, 2.18		
					>73.1	95	198	1.09	0.70, 1,68	0.60	
Rejnmark 2009[139]	Pre- and Post-menopausal	Breast Cancer(142 cases, 420 controls)	NR	25(OH)D	<60nmo/L	NR	NR	1.00	**Reference**		B
					60–84nmol/L	NR	NR	0.94	0.59, 1.47		
					>84nmol/L	NR	NR	0.52	0.32, 0.85	<0.05	
	Premenopausal				<60nmo/L	NR	NR	1.00	**Reference**		
					60–84nmol/L	NR	NR	0.59	0.26, 1.33		
					>84nmol/L	NR	NR	0.38	0.15, 0.97	<0.05	
	Postmenopausal				<60nmo/L	NR	NR	1.00	**Reference**		
					60–84nmol/L	NR	NR	1.20	0.67, 2.16		
					>84nmol/L	NR	NR	0.71	0.38, 1.30	>0.05	
Kuhn 2013[145] EPIC	40–65 years	Breast Cancer	4.1 yrs	25(OH)D	Q1: <=39.3	342	688	1.00	**Reference**	0.67	A
					Q2: 39.4–50.9	357	707	1.03	0.83, 1.29		
					Q3: 51.0–63.0	324	670	0.94	0.74, 1.19		
					Q4: >63.0	368	717	1.07	0.85, 1.36		
					log2 (continuous)	1391	2782	1.01	0.86, 1.19	0.86	

* Statistically significant (P<0.05)
[A] Total number of women not reported

Table 27b. Vitamin D and breast cancer: Results of prospective cohort studies (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Freedman 2007[103] NHANES III [17971526]	All Adults	Breast cancer mortality (28/ND)[A]	105 mo	25(OH)D	<63	20	ND	**1**	**Reference**	NS	B
					≥63	8	ND	HR 0.28	0.08, 0.93*		
NEW Studies											
Jacobs 2011 [144] Women's Healthy Eating and Living (WHEL)		Breast Cancer (512/3085)	NR	25(OH)D	<25 nmol/L(deficient)	nr	51	OR=1.14	0.57, 2.31		B
					≥25and <50 nmol/L(insufficient)	nr	282	1.00	0.68, 1.48		
					≥50 and <75 nmol/L(suboptimal)	nr	410	1.05	0.76, 1.47		
					≥75 nmol/L(optimal)	nr	281	1.00	**Reference**	0.85	
		Premenopausal			<25 nmol/L(deficient)	nr	6	0.17	0.01, 4.56		
					≥25and <50 nmol/L(insufficient)	nr	31	1.02	0.33, 3.16		
					≥50 and <75 nmol/L(suboptimal)	nr	45	1.76	0.64, 4.87		
					≥75 nmol/L(optimal)	nr	36	1.00	**Reference**	0.61	
		Postmenopausal			<25 nmol/L(deficient)	nr	37	1.45	0.62,3.37		
					≥25and <50 nmol/L(insufficient)	nr	202	1.09	0.68, 1.76		
					≥50 and <75 nmol/L(suboptimal)	nr	266	0.90	0.60, 1.36		
					≥75 nmol/L(optimal)	nr	187	1.00	**Reference**	0.49	
Eliassen 2011 [135] NHSIII		Breast Cancer (613 cases, 1218 controls)	NR	25(OH)D	Quartile 1(<46 nmol/L)	141	441	1.00	**Reference**		A
					Quartile 2(46.0 to 61.5 nmol/L)	151	456	1.05	0.79, 1.39		
					Quartile 3(61.5 to <76.5 nmol/L)	145	452	0.95	0.71, 1.29		
					Quartile 4 (≥76.5 nmol/L)	176	482	1.20	0.88, 1.63	0.320	
Ordonez-Mena 2013[97] ESTHER	50–74 years	Breast Cancer	8 yrs	25(OH)D	Q1	38	1464	1.08	0.72, 1.60		B
					Q2+Q3	71	2951	1.00	Reference		
					Q4	26	846	1.39	0.89, 2.18		

[A]Total number of women not reported

Table 27c. Vitamin D and breast density: Results of RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Bertone-Johnson, 2012[140] WHI Mammogram Density/Ancillary Study	50–79 years	percent mammographic density	1°	1 yr	(Vit D_3 400 IU+1,000 mg calcium)/day	179	%	3.7	final=3.6	2.9, 4.6	+0.8	-0.2, 1.8	0.1	A
					placebo	151	%	2.8	final=2.8	2.2, 3.7				
	Total vitamin D intake <200				(Vit D_3 400 IU+1,000 mg calcium)/day	87	%	3.6	final=3.5	2.5, 4.9	+0.5	-0.9, 1.9	0.47	
					placebo	77	%	3	final=3	2.1, 4.3				
	Total vitamin D intake >400				(Vit D_3 400 IU+1,000 mg calcium)/day	53	%	4.3	final=4	2.6, 6.0	+1.7	-0.1, 3.5	0.07	
					placebo	44	%	2.7	final=2.3	1.3, 4.2				
	Total vitamin D intake 200–<400				(Vit D_3 400 IU+1,000 mg calcium)/day	29	%	2.4	final=2.8	1.4, 5.6	-0.4	-2.5, 1.7	0.70	
					placebo	24	%	2.5	final=3.2	1.7, 6.1				

Note: Outcomes cells are shaded for the Control rows.

Table 27d. Vitamin D and breast density: Results of nested case-control studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Green 2010[141] Nurses' Health Study		percent mammogram-phic density	1°	within one year of blood collection	1,25(OH)$_2$D: 1st quartile (32.5– 72.8 nmol/l)	110	%	nr	Final=25.2					B
					1,25(OH)$_2$D: 2nd quartile (72.8 –82.8 nmol/)	108	%	nr	27.6		+2.1	nc		
					1,25(OH)$_2$D: 3rd quartile (82.8–93.3 nmol/l)	110	%	nr	23.3		-2.2	nc		
					1,25(OH)$_2$D: 4th quartile (93.5-140.5 nmol/l)	114	%	nr	25.8		+0.3	nc		
					25(OH)D: 1st quartile (cut points vary by batches)	118	%	nr	26.3					
					25(OH)D: 2nd quartile	115	%	nr	25.6		-0.7	nc		
					25(OH)D: 3rd quartile	124	%	nr	24.8		-1.5	nc		
					25(OH)D: 4th quartile	112	%	nr	25.7		-0.6	nc		

Pancreatic Cancer

Synopsis

No qualified systematic reviews evaluated associations between serum 25(OH)D concentrations and the incidence of pancreatic cancer. **A pooled nested case-control study within eight cohorts found an association between 25(OH)D concentration and pancreatic cancer (rated A).[146] Individuals with 25(OH)D concentration ≥100 nmol/L had greater risk of pancreatic cancer incidence compared to those with 25(OH)D <25 nmol/L (OR=2.24, 95% CI 1.22, 4.12**).

In the original report, two nested case-control studies, rated A in methodological quality, evaluated the association between serum 25(OH) concentration and the risk of developing pancreatic cancer in two different populations. One study found that older adult male smokers living in Finland with higher baseline serum 25(OH)D concentration had an increased risk of exocrine pancreatic cancer compared with those with lower concentration (>65.5 vs. <32 nmol/L; OR=2.92; P for trend=0.001). The other study found that baseline 25(OH)D concentrations were not associated with the risk of overall pancreatic cancer (>82.3 vs. <45.9 nmol/L; OR=1.45; P for trend=0.49) among older adults living in the United States. However, there was an increased risk of pancreatic cancer among the study participants with higher compared to lower 25(OH)D concentrations (>78.4 vs. <49.3 nmol/L; OR=4.03) only in those living in low residential UVB exposure areas but not among those living in moderate or high residential UVB exposure areas.

Detailed Presentation (Tables 28 & 29)

51–74 years

The pooled nested case-control study is based on 8 cohorts: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), CLUE, the Cancer Prevention Study II Nutrition Cohort (CPSII), the New York University Women's Health Study (NYU-WHS), the Multiethnic Cohort Study (MEC), the PLCO, and the Shanghai Women's and Men's Health Studies (SWHS and SMHS)[146]. The pooled sample contains 952 cases (median age 62, IQR 56–68) and 1,333 controls (median age 52, IQR 57–67). Serum 25(OH)D concentration was stratified into sextiles. The odds ratio for pancreatic cancer was 2.24 (95% CI 1.22, 4.12) comparing the 6th sextile (≥100 nmol/L) to the 1st sextile (<25 nmol/L). The result was adjusted for age, race/ethnicity, sex, cohort, date of blood draw, BMI, smoking status, and diabetes status.

In the original report, one nested case-control study based on the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) in older adult male smokers aged 54 to 62 years in Finland identified 200 cases of incident exocrine pancreatic cancer.[147] These cases were matched to 400 controls. Baseline serum 25(OH)D concentration was stratified into quintiles. The odds ratio for exocrine pancreatic cancer was 2.92 (95% CI 1.56, 5.48) comparing 5th quintile (>65.5 nmol/L) to 1st quintile (<32 nmol/L). The result was adjusted for age, month of blood drawn, years smoked, number of cigarettes smoked per day, reporting to have quit smoking more than three consecutive visits (>1 y) during the trial (1985–1993), occupational physical activity, education, and serum retinol. The study authors excluded islet cell carcinomas from analysis because the etiology for their pathogenesis might be different from that of exocrine tumors.

In the original report, another nested case-control study based on the Prostate, Lung, Colorectal, and Ovarian Screening (PLCO) trial in older men and women aged 55 to 74 years in the United States identified 184 cases of incident pancreatic cancer.[148] These cases were matched to 368 controls. Baseline serum 25(OH)D concentration was stratified into quintiles. The odds ratio for exocrine pancreatic cancer was 1.45 (95% CI 0.66, 3.15) comparing 5th quintile (>82.3 nmol/L) to 1st quintile (<45.9 nmol/L). The result was adjusted for age, race, sex, date of blood draw based on 2-month blocks, BMI and smoking. The association was not significantly modified by season of blood collection (P for interaction > 0.14); but estimated residential annual solar UVB exposure significantly modified the 25(OH)D concentration and pancreatic cancer association (P for interaction = 0.015). In the joint effects models, among subjects with low estimated annual UVB residential exposure, higher compared with lower 25(OH)D concentrations were associated with increased risk of pancreatic cancer (compared with the lowest quartile, the ORs for each respective quartile were 2.52, 2.33, and 4.03; 95% CI 1.38, 11.79), whereas among subjects with moderate to high residential UVB exposure, 25(OH)D concentrations were not associated with pancreatic cancer. There was no significant interaction of 25(OH)D concentration and pancreatic cancer by smoker status, sex, physical activity, or total vitamin A intake.

Findings by Life Stage

- **0–6 mo**
  not reviewed
- **7 mo–2 y**
  not reviewed
- **3–8 y**
  not reviewed
- **9–18 y**
  not reviewed
- **19–50 y**
  No study specifically targeted this age group.
- **51–70 y**
  One pooled nested case-control study within eight cohorts found that individuals with 25(OH)D concentration ≥100 nmol/L had greater risk of pancreatic cancer incidence compared to those with 25(OH)D <25 nmol/L (OR=2.24, 95% CI 1.22, 4.12). **In the original report,** one nested case-control study found that male smokers living in Finland with higher baseline serum 25(OH)D concentration had an increased risk of pancreatic cancer compared with those with lower concentration (5th vs. 1st quintile, >65.5 vs. <32 nmol/L: OR 2.92, 95% CI 1.56, 5.48, P for trend = 0.001). Another study found that baseline 25(OH)D concentrations were not associated with overall risk of pancreatic cancer among older adults living in the United States (5th vs. 1st quintile, >82.3 vs. <45.9 nmol/L: OR 1.45, 95% CI 0.66, 3.15; P for trend=0.49). However, there was an increased risk of pancreatic cancer among the study participants living in low residential UVB exposure areas (4th vs. 1st quartile >78.4 vs. <49.3 nmol/L: OR=4.03; 95% CI 1.38, 11.79).
- **≥71 y**
  No study specifically targeted this age group.

- **Postmenopause**
  not reviewed
- **Pregnant & lactating women**
  not reviewed

Table 28. Vitamin D and pancreatic cancer: Characteristics of observational studies (updated from original report)

Author Year Trial/Cohort Country (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						
						Nutrients	Demographic	Anthrop	Medical	UV Exposure	Lifestyles	Comments
Stolzenberg-Solomon 2006[147] ATBC Finland (60°N) [17047087]	Health status Mean age (range/SD), y Male (%)	All smokers 58 100	Assay Season blood drawn	RIA (DiaSorin) nd; but result adjusted for this variable	Exocrine pancreatic risk stratified by baseline 25(OH)D quintiles	X	X			X	X	
Stolzenberg-Solomon 2009[148] PLCO US (various) [19208842]	Health status Mean age (range), y Male (%)	DM: 10.5% 66 (55–74) 65.2	Assay Season blood drawn	RIA (Heartland Assays lab) All seasons	Pancreatic risk stratified by baseline 25(OH)D quintiles Pancreatic risk stratified by residential sun exposure levels and baseline 25(OH)D quartiles		X	X		X	X	
NEW Studies												
Stolzenberg-Solomon, 2010[146] Cohort Consortium Vitamin D Pooling Project or Rarer Cancers	Health status Mean age (SD), y Male (%)	nd nd (nd) 66.5%			Pancreatic risk stratified by baseline 25(OH)D sextiles							
Afzal 2013[99] Denmark	Health status Mean age (SD), y Male (%)	NR 58 (47–65) 45%			Pancreatic risk stratified by baseline 25(OH)D category		X	X			X	HR (95%CI) for pancreatic cancer are shown in Figure 1

Table 29. Vitamin D and pancreatic cancer: Results of observational studies (updated from original report)

Author Year Study Name [PMID]	Life Stage, y	Outcome (No. of Cases; No. of Control)	Time to Diagnosis, y	25(OH)D Concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
Stolzenberg-Solomon 2006[147] ATBC Finland (60°N) [17047087]	51–70, male only	Exocrine pancreatic cancer (200; 400)	11.8 (median)	<32	27	80	**1**	**Reference**	0.001	A
				32–41.1	34	80	1.3	0.70, 2.40		
				41.1–51.1	47	80	2.12	1.15, 3.90*		
				51.1–65.5	35	81	1.5	0.81, 2.76		
				>65.5	57	79	2.92	1.56, 5.48*		
Stolzenberg-Solomon 2009[148] PLCO US (various) [19208842]	51–70, both sexes	Pancreatic cancer (184; 368)	5.4 (median), up to 11 y	≤45.9	44	74	**1**	**Reference**	0.49	A
				>45.9 to ≤60.3	40	74	0.97	0.47, 1.98		
				>60.3 to ≤69.5	27	73	0.86	0.40, 1.84		
				>69.5 to ≤82.3	31	74	0.84	0.39, 1.80		
				>82.3	42	73	1.45	0.66, 3.15		
		Pancreatic cancer: Low residential sun exposure area (91; 167)	nd	<49.3	22	44	**1**	**Reference**	P for interaction between low and moderate/high residential sun exposure = 0.015	
				>49.3 to <65.2	22	42	2.52	0.92, 6.90		
				>65.2 to <78.4	21	43	2.33	0.83, 6.48		
				>78.4	26	38	4.03	1.38, 11.79*		
		Pancreatic cancer: Moderate residential sun exposure area (91; 167)	nd	<49.3	33	48	1.97	0.80, 4.82		
				>49.3 to <65.2	15	50	0.66	0.22, 2.01		
				>65.2 to <78.4	18	49	0.91	0.31, 2.71		
				>78.4	24	54	1.45	0.53, 3.96		

Table 29. Vitamin D and pancreatic cancer: Results of observational studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage, y	Outcome (No. of Cases; No. of Control)	Time to Diagnosis, y	25(OH)D Concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
NEW Studies										
Stolzenberg–Solomon 2010[146] Cohort Consortium Vitamin D Pooling Project or Rarer Cancers		Pancreatic Cancer (952 cases, 1333 controls)	nd	<25	115	256	1.00	**Reference**	0.14	A
				25 to <37.5	164	389	1.04	0.74, 1.44		
				37.5 to <50.0	208	494	1.10	0.79, 1.55		
				50.0 to <75.0	306	764	1.06	0.76, 1.48		
				75.0 to <100.0	120	310	1.08	0.73, 1.59		
				>100	39	69	2.24	1.22, 4.12		
Afzal 2013[99]		Pancreatic Cancer	28 yrs	25(OH)D, 50% reduction in plasma levels	109	9791	HR 1.05	0.84, 1.30		B

* Statistically significant (P<0.05)

Vitamin D and Immunologic Outcomes

We reviewed primary studies that evaluated relationships between vitamin D and any immune function related outcomes.

Synopsis

The current report identified five RCTs that assessed the effect of supplemental vitamin D on infectious illnesses and three cohort studies that assessed the association between vitamin D concentrations and risk for infectious illnesses. RCTs of infants and adults reported no significant effect of supplementation on the risk for upper respiratory infections; whereas one RCT conducted among 4-year-old Japanese children reported a positive effect of supplementation. Three prospective cohort studies observed an association between low cord blood 25(OH)D concentrations and increased risk for respiratory infections at 3 to 6 months of age, in New Zealand, South Korea, and the Netherlands. A Norwegian prospective study found an association between lower midpregnancy serum 25(OH)D and lower respiratory tract infections in the first 36 months of life. Two studies of school-age children, one in Colombia and one in Canada, observed associations between low serum 25A(OH)D and gastrointestinal tract infections and ear infections, and viral respiratory tract infections, respectively. A study of healthy U.S. adults found an association between serum concentrations of 25(OH)D levels of 95nmol/L or higher and reduced risk for acute respiratory viral infections. Studies of German and Finnish adults observed associations between lower serum 25(OH)D and respiratory disease mortality and pneumonia, respectively.

The current report identified one RCT that found no effect of prenatal vitamin D supplementation on the risk for wheeze, atopy, or eczema at 3 years of age. The report also identified five prospective cohort/nested case control studies that reported mixed associations of serum concentrations of 25(OH)D and risk for asthma, atopy, and/or eczema. An Australian study observed a significant association of cord blood 25(OH)D and risk for eczema but not allergies at 12 months of age. A prospective cohort study conducted in the UK found no association between maternal serum 25(OH)D at 34 weeks gestation and asthma, wheeze, and atopy in their children at 6 years of age. A prospective cohort study conducted in the Netherlands found that serum 25(OH)D concentrations at 4 years of age significantly predicted asthma and severe asthma at 8 years of age. Another UK longitudinal study found a small but significant association of wheeze and antecubital dermatitis in 10-year old children with serum levels of 25(OH)D2 but a negative association with 25(OH)D3. Finally, the HUNT study, a large population health survey in Norway, found no association of 25(OH)D with asthma in women and only a weak association in men that disappeared when adjusted for confounders.

The current report identified one RCT and four prospective cohort studies on the risk for autoimmune disease. A substudy of the WHI CaD trial found no effect of supplementation on women's risk for rheumatoid arthritis. Two nested case control studies and one cohort study assessed the association between maternal serum 25(OH)D concentrations or subsequent childhood or adult status with risk for type 1 diabetes mellitus and reported mixed findings. One study assessed the effects of maternal 25(OH)D concentrations on the risk for multiple sclerosis (MS) in the offspring and also assessed the

effect of 25(OH)D concentrations across the adult population on the risk for subsequent MS and found mixed effects.

In the original report, analyses using NHANES III data (general adult populations living in the United States) showed no significant association between baseline 25(OH)D concentrations and infectious disease mortality.

One cohort study from UK suggested a relationship between maternal 25(OH)D concentration and the risk of eczema in their children, but the analysis did not control for important potential confounders, and the 25(OH)D concentrations in children were not measured.

Detailed Presentation (Tables 30a-d & 31a-d)

Infection. The current report identified five RCTs that assessed the effect of supplemental vitamin D on infectious illnesses and nine cohort studies that assessed the association between 25(OH)D concentrations and risk for infectious illnesses.

A RCT in Afghanistan that randomized infants to 100,000IU every 3 months for 18 months or to placebo found no effect of supplementation on the incidence of pneumonia or subsequent episodes of pneumonia (rated A).[149] A U.S. RCT that randomized healthy adults 18 to 80 years of age to 2000IU vitamin D per day or placebo for 3 months reported no effect of supplementation on the incidence or duration of upper respiratory infections (rated B).[150] A Finnish study that randomized male soldiers, 18 to 28 years of age, to 400IU vitamin D per day or placebo for 6 months reported no effect on the acute prevalence of respiratory infection or self-reported cold symptoms but a small significant effect on the number of soldiers who had no days absent from duty (adjusted OR 1.89 [1.01, 3.54](rated B).[151] The VIDARIS Study, a New Zealand RCT of 322 adults 18 years of age and older (mean age 47, 25% men) that randomized individuals to an initial 200,000 IU oral dose of vitamin D_3, then 200,000 IU 1 month later, then 100,000 IU monthly or placebo for 18 months found no effect on the number of upper respiratory infections, days of work missed, or duration of symptoms (rated A).[152]

Nine prospective cohort studies were also identified for the current report that assessed the association of prenatal or baseline 25(OH)D concentrations with risk for infectious illness incidence or mortality.

A prospective cohort study in the Netherlands followed 156 infants from birth to 6 months of age and observed an association between low cord blood 25(OH)D concentrations and increased risk for respiratory syncytial virus bronchiolitis infections (rated B).[153] A prospective cohort study in New Zealand followed a group of infants from birth and found an association of low cord blood serum 25(OH)D status with increased risk for respiratory infection at 3 months of age(rated B).[154] A study in South Korea (the COCOA study) followed 525 newborns from birth to 6 months of age and found an association between low maternal cord blood 25(OH)D concentrations and increased risk for viral respiratory tract infections (p=0.0004) (rated B).[155] A Norwegian prospective cohort study (MoBa) followed 1248 infants from birth to 36 months and observed an association between increasing midpregnancy maternal 25(OH)D concentrations and decreasing frequency and number of lower respiratory tract infections (rated B).[156]

A prospective cohort study of 475 school-age children, the Bogota School Children Cohort, observed an association between lower baseline serum 25(OH)D and increased risk for gastrointestinal tract infections (RR 2.05) and ear infections (RR 2.36) (rated B).[157] A

prospective cohort study in Canadian Hutterite communities followed 743 children 3 to 15 years of age for 6 months and found that younger age and lower serum 25(OH)D levels were associated with increased risk for viral RTI: Serum 25(OH)D levels <75 nmol/L increased the risk of viral RTI by 50% (hazard ratio [HR], 1.51; 95% confidence interval [CI], 1.10–2.07, P=.011) and levels <50 nmol/L increased the risk by 70% (HR, 1.67; 95% CI, 1.16–2.40, P=.006).[158]

A study of healthy U.S. adults followed for 4 months found an association between serum concentrations of 25(OH)D levels of 95nmol/L or higher and reduced risk for acute respiratory viral infections (rated A).[159] The ESTHER Study of 9,578 German adults observed an association between vitamin D deficiency (defined by the authors as less than 30nmol/L) and an increased risk for respiratory disease mortality (HR2.50, 1.12, 5.56) (rated B).[76] The Kuipio IHD Risk Factor Study, which followed 1,421 Finnish adults 53 to 73 years of age for 10 years, found a 2.6-fold increased risk for pneumonia in the lowest compared with the highest tertile of serum 25(OH)D (rated B).[160]

<u>Asthma, Atopy, and Eczema</u>. The current report identified one RCT and five prospective studies on the association between serum 25(OH)D and risk for asthma, atopy, and/or eczema. A UK RCT randomized 180 pregnant women at 27 weeks gestation to receive 0 or 800IU vitamin D daily for the remainder of pregnancy or one oral bolus of 20,000IU; at 3 years of age, no significant differences were seen among 158 offspring in their risk for ever having experienced wheeze, atopy, or eczema (rated A).[161]

An Australian cohort study measured maternal and cord blood and found a significant association between cord blood 25(OH)D and decreased risk for eczema at 12 months of age. No association was seen with the results of skin prick tests for environmental and food allergies and IgE testing for food allergy.[162]

A UK prospective study that followed 860 mother-infant pairs found no association between maternal serum 25(OH)D at 34 weeks gestation and the incidence of asthma, wheeze, or atopy at 6 years of age.[163]

A longitudinal study in the Netherlands (PIAMA) is assessing associations of nutritional indicators with the risk for asthma in a large birth cohort. The most recent data suggest that rates of asthma and severe asthma at 8 years of age are higher among those whose serum 25(OH)D concentrations were in the lowest or middle tertile at 4 years of age.[164]

The Avon Longitudinal Study of Parents and Children, a UK study, measured serum 25(OH)D2 and D3 (using HPLC/ tandem mass spectrometry) in some 14,500 children and found an association between lower levels of 25(OH)D2 at a mean age of 9.8 years and higher levels of wheeze, poor lung function, and flexural (antecubital) dermatitis at a mean age of 15.5 years; higher levels of 25(OH)D3 were associated with increased incidence of flexural dermatitis and wheezing but were not associated with lung function. Although the authors adjusted for confounders, they cautioned about interpreting the results without conducting trials.[165]

The HUNT study analyzed the association of baseline vitamin D (and other nutrient) status in adults with the risk for asthma 11 years later using data from a large-scale longitudinal survey of health in Norway. They found no association of 25(OH)D concentrations with subsequent risk for asthma among women and a small association in men that disappeared after adjustment for confounders.[166]

<u>Autoimmune.</u> The current report identified one RCT, three nested case control studies, and one prospective cohort study on the risk for autoimmune disease. A substudy of the

WHI CaD trial that assessed participants at 5.1 years found no effect of supplementation with 400IU vitamin D and 1000mg calcium on women's risk for rheumatoid arthritis (rated A).[167] A nested case control study among U.S. Navy and Marine Corps military personnel observed an association of Type 1 diabetes mellitus (DM) with serum 25(OH)D status at enlistment (310 cases and 310 matched controls) among white soldiers but not among black or Hispanic soldiers (rated B).[168] A nested case control study conducted in Norway observed a trend toward an increasing association of type 1 DM in the first 15 years of life and decreased maternal 25(OH)D concentrations (rated C).[169] A U.S. prospective cohort study of children at increased risk for developing Type 1 DM based on an Islet Autoimmune genetic marker, found no association of 25(OH)D concentrations at 9 months of age and subsequent risk for progression to DM(rated B). GRoMS, a nested case control study among individuals in Sweden who developed multiple sclerosis, found no association with maternal serum 25(OH)D concentrations but a possible association of adult levels with subsequent risk for the disease (rated B).[170]

In the original report, one study analyzed NHANES III data and showed no association between baseline 25(OH)D concentrations and infectious disease.[85] NHANES III cohort represents general adult populations living in the United States. This study was rated quality C.

One cohort study from UK analyzed the serum 25(OH)D concentration in 440 white women in late pregnancy (~33 wk) and found their infants' risk of eczema at age 9 months was higher in those mothers in the top quartile of the distribution of serum 25(OH)D (>50 nmol/L) compared with those at the bottom quartile (<30 nmol/L), although the results were not statistically significant.[55] However, this analysis did not control for important potential confounders, and the 25(OH)D concentrations in children were not measured. This study was rated quality C.

Findings by Life Stage

- **0–6 mo**
  No data **in original study. A RCT in Afghanistan that randomized infants to 100,000IU every 3 months for 18 months or to placebo found no effect of supplementation on the incidence of pneumonia or subsequent episodes of pneumonia. A prospective cohort study in South Korea that followed 525 infants from birth to 6 months of age observed a significant association of low cord blood 25(OH)D and increased risk for respiratory tract infection. A prospective cohort study in the Netherlands followed 156 infants from birth to 6 months of age and observed an association between low cord blood 25(OH)D concentrations and increased risk for respiratory syncytial virus bronchiolitis infections. A prospective cohort study in New Zealand followed a group of infants from birth and found an association of low cord blood serum 25(OH)D concentrations with increased risk for respiratory infection at 3 months of age.**
- **7 mo–2 y**
  No data **in original study. A RCT in the UK that randomized pregnant women at 27 weeks gestation to receive 0 or 800IU vitamin D daily for the remainder of pregnancy or one oral bolus of 20,000IU; at 3 years of age, no significant differences were seen among 158 offspring in their risk for ever having experienced wheeze, atopy, or eczema. A prospective cohort study in Norway that followed 1,248 children from birth to 36 months of age observed a significant association between maternal serum 25(OH)D at midpregnancy and the number and frequency of lower**

respiratory tract infections. An Australian cohort study measured maternal and cord blood and found a significant association between cord blood 25(OH)D and decreased risk for eczema at 12 months of age. No association was seen with the results of skin prick tests for environmental and food allergies and IgE testing for food allergy.[162]

- **3–8 y**
  No **data in original study**. **A RCT in Japan that randomized 344 3-year-old nursery school children to 1200IU vitamin D per day or placebo found a significant decrease in the incidence of Influenza A among supplemented children after 4 months; the effect was greater in children receiving no other vitamin supplementation at baseline. A prospective study that followed 475 Colombian school-age children for 1 year found an association between baseline serum 25(OH)D and risk for gastrointestinal and ear infections.**[157] **A prospective study that followed 743 children (3 to 15 years of age) in Canadian Hutterite communities for 6 months observed an association between vitamin D deficiency and insufficiency and risk for viral respiratory tract infections.**[158] **A UK prospective study that followed 860 mother-infant pairs found no association between maternal serum 25(OH)D at 34 weeks gestation and the incidence of asthma, wheeze, or atopy at 6 years of age.**[163] **A longitudinal study in the Netherlands (PIAMA) is assessing associations of nutritional indicators with the risk for asthma in a large birth cohort. The most recent data suggest that rates of asthma and severe asthma at 8 years of age are higher among those whose serum 25(OH)D concentrations were in the lowest or middle tertile at 4 years of age.**[164]
- **9–18 y**
  No data in original study. **The Avon Longitudinal Study of Parents and Children, a UK study, measured serum 25(OH)D2 and D3 (using HPLC/ tandem mass spectrometry) in some 14,500 children and found an association between lower levels of 25(OH)D2 at a mean age of 9.8 years and higher levels of wheeze, poor lung function, and flexural (antecubital) dermatitis at a mean age of 15.5 years; higher serum concentration of 25(OH)D3 were associated with higher incidence of flexural dermatitis and wheezing but were not associated with lung function. A nested case control study conducted in Norway observed a trend toward an increasing association of type 1 DM in the first 15 years of life and decreased maternal 25(OH)D concentrations. A U.S. prospective cohort study of children at increased risk for developing Type 1 DM based on an Islet Autoimmune genetic marker, found no association of 25(OH)D concentrations at 9 months of age and subsequent risk for progression to DM.**
- **19–50 y**
  Three RCTs found no effect of supplemental vitamin D on the risk for respiratory infections among adults. The HUNT study analyzed the association of baseline vitamin D (and other nutrient) status in adults with the risk for asthma 11 years later using data from a large-scale longitudinal survey of health in Norway; they found no association of 25(OH)D concentrations with subsequent risk for asthma among women and a small association in men that disappeared after adjustment for confounders. A nested case control study among U.S. Navy and Marine Corps military personnel observed an association of Type 1 diabetes mellitus (DM) with

serum 25(OH)D concentrations at enlistment (310 cases and 310 matched controls) among white soldiers but not among black or Hispanic soldier. The original report identified NHANES III data **that** include people in this life stage. Analyses using NHANES III data (general adult populations living in the United States) showed no significant association between baseline 25(OH)D concentrations and infectious disease mortality.

- **51–70 y**
  NHANES III data also include people in this life stage. **The German prospective ESTHER study identified for the current report observed a significant inverse association between serum 25(OH)D concentrations and risk for respiratory disease mortality among adults 50 to 74 years of age. The Finnish Kuipio IHD Risk Factor Study observed an increased risk for pneumonia among the adults, 53 to 73 years of age in the lowest tertile of serum 25(OH)D.**
- **≥71 y**
  NHANES III data also include people in this life stage
- **Postmenopause**
  No data **found in the original report**. **The current report identified a substudy of the WHI CaD trial that assessed participants at 5.1 years and found no effect of supplementation with 400IU vitamin D and 1000mg calcium on women's risk for rheumatoid arthritis**
- **Pregnant & lactating women**
  Studies identified for the current report are described above for 0–6 months. One cohort study from UK identified in the original report analyzed the serum 25(OH)D concentration in white women in late pregnancy (~33 wk) and showed a relationship between maternal 25(OH)D concentration and the risk of eczema in their children. However, this analysis did not control for important confounders, and the 25(OH)D concentrations in children were not measured.

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Melamed 2008[85] NHANES III US (various) [18695076]	• Health status	DM 7.4%, history of CVD 7.9%, HTN 25%	• Assay method	RIA (DiaSorin)	Infectious disease mortality stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	
	• Mean age (range), y	45 (≥20)										
	• Male (%)	46	• Season blood drawn	All								
Gale 2008[55] PAHSG UK (50ºN) [17311057]	• Health status	singleton pregnancy <17 wk	• Assay method	RIA	Length and weight in offspring stratified by mother's 25(OH)D		X			X		White only
	• Mean age (range/SD), y	26.3										
	• Male (%)	0	• Season blood drawn	nd								

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
NEW Studies											
Jones 2012[162] Perth, Australia	• Health status • Mean age (SD), y • Male (%)	Healthy 33.4 (SD 4.5) 51.5%		Eczema stratified by baseline 25(OH)D levels		X			X		Age, race= of mothers
Mai, 2012[166] HUNT Study Nord-Trondelag, Norway	• Health status • Mean age (SD), y • Male (%)	nd 39.7 (8.5) 43%		Asthma stratified by baseline 25(OH)D quartiles		X	X		X	X	Age= women controls
Pike, 2012[163] UK	• Health status • Mean age (SD), y • Male (%)	nd 30.37 (3.81), y 51.74%		Asthma stratified by baseline 25(OH)D levels	X	X	X		X		
Tolppanen, 2013[165] UK, Southwest England	• Health status • Mean age (SD), y • Male (%)	nd 9.84 (SD 0.02) 52.1		Asthma stratified by baseline $25(OH)D_2$ and $25(OH)D_3$ tertiles							

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
van Oeffelen, 2011[164] Netherlands	• Health status • Mean age (SD), y • Male (%)	nd nd (nd) 51.9%		Asthma stratified by baseline 25(OH)D tertiles		X				X	
NEW Nested case-control studies—Immune Function—Autoimmune Disease											
Munger, 2013[168] US	• Health status • Mean age (SD), y • Male (%)	Presumed healthy 20.6 (4.0) 95.1%		Type 1 Diabetes Mellitus stratified by baseline 25(OH)D tertiles							
Salzer 2012[170] Risk of Multiple Sclerosis Gestational Risk factors of Multiple Sclerosis (GRoMS) Sweden	• Health status • Mean age (Range), y • Male (%)	nd 26 (16–60) 7.8%		Multiple Sclerosis stratified by baseline 25(OH)D medians							

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Sorensen, 2012[169] Norway	• Health status • Mean age (SD), y • Male (%)	nd 9 (SD 3.6) 51%		Type 1 Diabetes stratified by baseline 25(OH)D quartiles		X			X		
NEW Cohort study—Immune Function—Autoimmune Disease											
Simpson, 2011[171] Diabetes Autoimmunity Study in the Young (DAISY) US Denver, CO	• Health status • Mean age (SD), y • Male (%)	At increased risk for Type 1 Diabetes 11.9 (4.4) 49%		Islet Autoimmune stratified by baseline 25(OH)D levels		X					
NEW Cohort study—Immune Function—Infectious Diseases											
Belderbos, 2011[153] Utrecht, Netherland	• Health status • Mean age (SD), y • Male (%)	Healthy 0.77 (0.13) 56%		Respiratory Syncytial Virus Bronchiolitis stratified by 25(OH)D tertiles			X				

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Camargo, 2011[154] Wellington (41°S latitude) and Christchurch (43°S latitude), New Zealand	• Health status • Mean age (SD), y • Male (%)	nd 0.77 (nd) 51%		Infection and Asthma stratified by 25(OH)D tertiles		X		X	X	X	
Sabetta, 2010[159] US Greenwich, CT	• Health status • Mean age (range), y • Male (%)	Healthy nd (20–88) 43%		Acute Viral Respiratory Tract Infections stratified by 25(OH)D medians	X	X	X				
Shin 2013[155] Cohort for Childhood Origin of Asthma and allergic diseases (COCOA) Korea	• Health status • Mean age (SD), y • Male (%)	NR Maternal age: 32.2 (SD 3.4) Newborns Range: (0–6) months Mothers: 0% Newborns: 53.1%		Respiratory tract infections, Acute nasopharyngitis, otitis media, and bronchiolitis stratified by 25(OH)D tertiles	X				X	X	

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Science 2013[158] Canada	• Health status • Mean age (SD), y • Male (%)	NR 9.3 (SD 3.4) 47.5%		Respiratory tract infections stratified by 25(OH)D medians		X					
Schottker 2013[76] ESTHER Germany	• Health status • Mean age (SD), y • Male (%)	NR 62 (SD 6.5) 43.8%		Respiratory disease mortality stratified by 25(OH)D tertiles	X	X		X	X	X	
Thornton 2013[157] Bogotá School Children Cohort Bogota, Columbia	• Health status • Mean age (SD), y • Male (%)	~7–12.5% stunted 8.9 (SD 1.6) 48%		Earache/discharge with fever and Cough with fever stratified by 25(OH)D tertiles		X					
Magnus 2013[156] Norwegian Mother and Child Cohort Study Norway	• Health status • Mean age (SD), y • Male (%)	NR NR 0%		Asthma stratified by 25(OH)D quartiles	X	X	X	X	X	X	

Table 30a. Vitamin D (mother) and immunologic outcomes (offspring): Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Aregbesola 2013[160] Kuopio Ischemic Heart Disease Risk Factor (KIHD) study Kuopio, Finland	• Health status • Mean age (SD), y • Male (%)	NR 62.5 (SD 6.5) 50.9%		Pneumonia stratified by 25(OH)D tertiles	X	X	X		X	X	

Table 30b. Vitamin D and immunologic outcomes: Characteristics of autoimmune disease RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Racovan, 2012[167] WHI US	• Health status • Mean age (range/SD), y • Male (%)	Post-menopausal 62.34 (SD 6.91) 0%		Rheumatoid Arthritis (RA) stratified by mother's 25(OH)D medians							

Table 30c. Vitamin D and immunologic outcomes: Characteristics of infectious disease continuous RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Li-Ng, 2009[150] US Long Island, NY	• Health status • Mean age (range/SD), y • Male (%)	nd 58.1 (SD 13.4) 20.3%		Duration of Upper Respiratory Tract stratified by 25(OH)D levels							
Laaksi, 2010[151] Pori Brigade, Finland	• Health status • Mean age (SD), y • Male (%)	Healthy Nd (nd) 100%		Days absent from duty stratified by 25(OH)D_3 levels		X					

Table 30d. Vitamin D and immunologic outcomes: Characteristics of infectious disease dichotomous RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Laaksi, 2010[151] Pori Brigade, Finland	• Health status • Mean age (range/SD), y • Male (%)	Healthy Nd (nd) 100%		Days absent from duty and self-reported cold symptoms stratified by 25(OH)D_3 levels		X					
Li-Ng, 2009[150]	• Health status • Mean age (SD), y • Male (%)	nd 58.1 (SD 13.4) 20.3%		Upper respiratory tract stratified by 25(OH)D medians							
Manaseki-Holland, 2012[149] Kabul, Afghanistan	• Health status • Mean age (SD), y • Male (%)	nd nd (nd) 52%		Pneumonia stratified by 25(OH)D_3 medians							Age groups reported but not mean age, only father's ethnicity reported
Murdoch, 2012[152] VIDARIS New Zealand	• Health status • Mean age (SD), y • Male (%) • Mean age (SD), y • Male (%)	nd 48 (10) 25% 10.4 (2.4) 55%		Days of missed work per episode stratified by 25(OH)D_3 and Placebo medians							
NEW Studies											
Goldring 2013[161] UK	• Health status • Mean age (SD), y • Male (%)	NR 3 44%		Wheeze ever and lower respiratory tract infection stratified by 25(OH)D medians	X	X				X	Children of mothers enrolled in a 3-arm RCT of vitamin D administration were prospectively followed

Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Melamed 2008[85] NHANES III US (various) [18695076]	Adults, both sexes	Infectious disease mortality (N=13,331)	Median 8.7 (IRQ 7.1–10.2) y	25(OH)D	<44	nd	13331 (Total)	0.84	0.38, 1.86	nd	C
					44–60	nd	nd	0.87	0.43, 1.74		
					61–80	nd	nd	1.01	0.53, 1.93		
					>80	nd	nd	**1**	**Reference**		
Gale 2008[55] PAHSG UK (54°N) [17311057]	Pregnant women; infant at 9 mo	Atopic eczema at 9 mo (48/440; 0.11)	9 mo	Maternal 25(OH)D at late pregnancy	<30 (Quartile)	9	440 (total)	**1**	**Reference**	nd	C
					30–50	10		1.11[A]	0.43, 2.84		
					50–75	15		1.75[A]	0.73, 4.17		
					>75	14		1.62[A]	0.67, 3.89		
NEW Studies—Allergy/Asthma											
Jones 2012[162]	Pregnant or lactating women, non-smoking	eczema	NR	$25(OH)D_3$	per 10 nmol/L rise in CB $25(OH)D_3$	78	231	OR=0.857	0.739, 0.995	0.042	A
Mai 2012[166]	Female 19–65 yrs	asthma	11 yrs	25(OH)D	≥75.0	81	328	OR=1.00	**Reference**		A
					50.0–74.9	125	555	0.8	0.57, 1.13		
					<50.0	170	566	0.94	0.67, 1.32		
					each 25-nmol/L reduction	376	1449	0.97	0.85, 1.12		
	Male 19–65 yrs				≥75.0	33	247	1.00	**Reference**		
					50.0–74.9	77	384	1.5	0.95, 2.38		
					<50.0	98	462	1.47	0.93, 2.32		
					each 25-nmol/L reduction	208	1093	1.14	0.94, 1.37		

Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Pike 2012[163]		current doctor-diagnosed asthma	6 yrs	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	87	836	RR=0.98	0.92, 1.04	0.56	B
		current wheeze in last 12 months				117	833	0.99	0.94, 1.05	0.76	
		any wheeze at or before 6 years				504	823	1.00	0.98, 1.02	0.95	
		transient wheeze				367	707	1.00	0.98, 1.02	0.89	
		persistent late wheeze				137	475	0.98	0.94, 1.03	0.49	
		persistent late wheeze with atopy				46	251	0.91	0.84, 0.99	0.04	
		persistent late wheeze without atopy				48	253	1.01	0.94, 1.09	0.73	
Tolppanen 2013[165]		wheezing	1 yrs	25(OH)D_2	per doubling of exposure	141	3323	OR=0.83	0.68, 1.00		B
		asthma				464	3323	0.89	0.78, 1.02		
		flexural dermatitis				300	3748	0.83	0.72, 0.94		
		wheezing	1 yrs	25(OH)D_3	per doubling of exposure	141	3323	1.14	1.03, 1.28		
		asthma				464	3323	1.02	0.93, 1.12		
		flexural dermatitis				300	3748	1.09	1.00, 1.18		

Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
van Oeffelen 2011[164]		bronchial hyperresponsiveness	8 yrs	25(OH)D	Tertile 1: range 23.1–60.2 nmol/L	80	204	OR=1.00	**Reference**		A
					Tertile 2: range 60.7–78.8 nmol/L	88	209	1.16	0.62, 2.18		
					Tertile 3: range 79.0–303.8 nmol/L	87	194	1.19	0.63, 2.23		
		atopy			Tertile 1: range 23.1–60.2 nmol/L	93	346	1.00	**Reference**		
					Tertile 2: range 60.7–78.8 nmol/L	101	237	2.19	1.17, 4.12		
					Tertile 3: range 79.0–303.8 nmol/L	93	279	1.23	0.64, 2.39		
		asthma	5–8 yrs	25(OH)D	Tertile 1: range 23.1–60.2 nmol/L	NR	NR	1.00	**Reference**		
					Tertile 2: range 60.7–78.8 nmol/L	NR	NR	0.97	0.57, 1.65		
					Tertile 3: range 79.0–303.8 nmol/L	NR	NR	0.68	0.39, 1.19		
		severe asthma			Tertile 1: range 23.1–60.2 nmol/L	NR	NR	1.00	**Reference**		
					Tertile 2: range 60.7–78.8 nmol/L	NR	NR	1.06	0.59, 1.90		
					Tertile 3: range 79.0–303.8 nmol/L	NR	NR	0.61	0.32, 1.15		
NEW Nested case-control studies—Immune Function—Autoimmune Disease											
Munger 2013[168]	US Navy, MC active duty	Type 1 Diabetes Mellitus	5.4 yrs	25(OH)D	<75nmol/L	45	102	RR =1	**Reference**		B
					75–<100nmol/L	76	236	0.6	0.38, 0.97		
					≥100nmol/L	65	220	0.56	0.35, 0.90	0.03	

Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Salzer 2012 Risk of Multiple Sclerosis[170]	0–6 mos 19–50 yrs	Multiple Sclerosis	NR	25(OH)D	≥75nmol/l	192	576	OR =0.39	0.16, 0.98		
					<75nmol/l			1	**Reference**	NR	A
Gestational Risk factors of Multiple Sclerosis (GRoMS)[170]					≥75nmol/l	37	222	1.8	0.53, 5.8		
					<75nmol/l			1	**Reference**	NR	A
Sorensen 2012[169]	Pregnant	Type 1 Diabetes	NR	25(OH)D	<55nmol/L	39	94	OR= 2.38	1.12, 5.07		
					>54 to 59nmol/L	31	88	1.78	0.85, 3.74		B
					>69nmol/L to 89nmol/L	22	75	1.35	0.63, 2.89		
					>89nmol/L	17	71	1	**Reference**	0.031	
NEW Cohort study—Immune Function—Autoimmune Disease											
Simpson 2011[171]	3–8 yrs	Islet Autoimmune (IA)	9 mos	25(OH)D	Inadequate (≤50)	30	128	HR=0.72	0.24,2.71	0.56	A
					Adequate (>50)			**1.00**	**Reference**		
Diabetes Autoimmunity Study in the Young (DAISY)		Type 1 Diabetes	NR	25(OH)D	Inadequate (≤50)	55	185	HR=0.44	0.14, 1.45	0.18	A
					Adequate (>50)			**1.00**	**Reference**		
NEW Cohort studies—Immune function—Infectious Diseases											
Belderbos 2011[153]	0–6 months	Respiratory Syncytial Virus Bronchiolitis	NR	25(OH)D	<50nmol/L	36		RR= 6.2	1.6, 24.9		
					50–74nmol/L	48		1.3	NR		A
					≥75nmol/l	72		1	**Reference**	0.13	

Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Camargo 2011[154]	0–6 months	Respiratory Infection	NR	25(OH)D	≥75nmol/L	NR	NR	OR= 1	**Reference**		B
					25–74nmol/L	NR	NR	1.35	0.88, 2.08		
					<25nmol/L	NR	NR	2.04	1.13, 3.67	0.03	
		Any Infection			≥75nmol/L	NR	NR	OR= 1	**Reference**		
					25–74nmol/L	NR	NR	1.49	0.92, 2.43		
					<25nmol/L	NR	NR	2.36	1.17, 4.73	0.02	
	15 mos	Wheeze			per 10nmol/L	331	NR	OR=0.98	0.93, 1.02	0.3	
	3 yrs				per 10nmol/L	472	NR	0.96	0.91, 1.00	0.04	
	5 yrs				per 10nmol/L	533	NR	0.95	0.91, 0.99	0.04	
	5 yrs	Incident asthma			per 10nmol/L	181		OR =1.03	0.97, 1.10	0.02	
Sabetta 2010[159]	19–50 yrs	Acute Viral Respiratory Tract Infections	4 months	25(OH)D	≥95 nmol/L	3	18	OR= 0.24	0.07, 0.87		A
					<95 nmol/L	81	180	1	**Reference**	0.015	
Shin 2013[155] Cohort for Childhood Origin of Asthma and allergic diseases (COCOA)		respiratory tract infections	6 months	25(OH)D	<25.0	74	180	3.41	1.57, 7.42	0.0008	B
					25.0–74.9	89	292	2.14	1.00, 4.58		
					>=75.0	9	53	1.00	**Reference**		
		acute nasopharyngitis			<25.0	67	180	4.64	1.88, 11.44	0.0002	
					25.0–74.9	75	292	2.71	1.11, 6.59		
					>=75.0	6	53	1.00	**Reference**		
		otitis media			<25.0	10	180	3.06	0.38, 24.46	0.3625	
					25.0–74.9	18	292	3.42	0.45, 26.15		
					>=75.0	1	53	1.00	**Reference**		
		bronchiolitis			<25.0	9	180	2.74	0.34, 22.11	0.4819	
					25.0–74.9	19	292	3.62	0.47, 27.63		
					>=75.0	1	53	1.00	**Reference**		

Table 31a. Vitamin D (mother) and immunologic outcomes (offspring): Results of observational studies (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Science 2013[158]		respiratory tract infections	156 days	25(OH)D	per 1-unit change in log levels	229	743	0.52	0.35, 0.79	0.002	B
					<25		4	0.72	0.13, 3.94	0.7	
					>=25		739	1.00	**Reference**		
					<50		152	1.54	1.07, 2.21	0.021	
					>=50		591	1.00	**Reference**		
					<75		565	1.35	1.01, 1.82	0.043	
					>=75		178	1.00	**Reference**		
Schottker 2013[76] ESTHER		respiratory disease mortality	9.5 yrs	25(OH)D	<30	13	1439	NR	NR		B
					30–50	26	4188	NR	NR		
					>50	16	3927	1.00	**reference**		
Thornton 2013[157] Bogotá School Children Cohort		earache/discharge with fever	140 days	25(OH)D	Deficient: <50	nr	48	2.36	1.26, 4.44		B
					Insufficient: 50–<75	nr	222	0.35	0.19, 0.65		
					Sufficient: >=75	nr	205	1.00	**Reference**		
		cough with fever			Deficient: <50	nr	48	0.77	0.57, 1.04		
					Insufficient: 50–<75	nr	222	0.53	0.44, 0.65		
					Sufficient: >=75	nr	205	1.00	**Reference**		
Magnus 2013[156] Norwegian Mother and Child Cohort Study		asthma	36 mos	25(OH)D	20 nmol/L increase in 25(OH)D	489	1672	0.91	0.81, 1.02		B
					<51	114	316	1.00	**Reference**		
					51–75	187	584	0.84	0.61, 1.17		
					>75	188	771	0.67	0.48, 0.95		
Aregbesola 2013[160] Kuopio Ischemic Heart Disease Risk Factor (KIHD) study		pneumonia	9.8 yrs	25(OH)D3	Tertile 1: 8.9–33.8						B
					Tertile 2: 33.9–50.7						
					Tertile 3: 50.8–112.8						
						38	925	2.4	1.2, 4.9		
						22	426	1.4	0.7, 2.8		
						13	70	1.0	**Reference**		

[A] Crude OR

Table 31b. Vitamin D and immunologic outcomes: Results of autoimmune disease RCTs (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Racovan 2012[167] WHI	Postmenopause	Rheumatoid Arthritis	5.1 yrs	Vit D	400IU + Ca 1000ng	45	16283	HR 1.15	0.75, 1.75	0.53	A
					Placebo	41	16238	HR 1	**Reference**		

Table 31c. Vitamin D and immunologic outcomes: Results of infectious disease RCTs (continuous outcomes) (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration	Intervention	No. Analyzed	Final mean	Final SD	Net Diff	Net Diff 95% CI	Study Quality
Li-Ng 2009[150]	18–80 years	Duration of Upper Respiratory Tract	12 wks	Vit D 2000IU/day	78	5.4	4.8	+1.0	-1,2, 1.4	B
				Placebo	70	5.3	3.1	Reference		
Laaksi 2010[151]	18–28 years	Days absent from duty	6 mos	Vit D3 400 IU	80	2.2	3.2	-0.8	-1.9, 0.3	B
				Placebo	84	3.0	4.0	Reference		

Table 31d. Vitamin D and immunologic outcomes: Results of infectious disease RCTs (dichotomous outcomes) (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Intervention	No. of Events	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Laaksi 2010[151]	18–28 years	Self-reported common cold symptoms	6 months	Vit D3	400 IU	45	80	OR 1.17	0.63, 2.16	0.619	B
				Placebo	Placebo	44	84	1	**Reference**		
		No days absent from duty		Vit D3	400 IU	41	80	1.89	1.01, 3.54	0.045	
				Placebo	Placebo	30	84	1	**Reference**		
Li-Ng 2009[150]	18–80 years	Upper Respiratory Tract	12 weeks	Vit D	2000IU/day	28	78	OR 0.79	0.41, 1.54	0.61	B
					Placebo	29	70	1	**Reference**		
Manaseki-Holland 2012[149]	infants aged 1–11 months	All Pneumonia First episode	NR	Vit D3	100,000IU	260	1782 person years	IRR =1.065	0.895, 1.268	0.476	A
					Placebo	2445	1782 person years	1	**Reference**		
		All Pneumonia repeat episode			100,000IU	138	2031 person years	IRR =1.685	1.282, 2.212	<0.0001	
					Placebo	82	2027 person years	1	**Reference**		
Murdoch 2012[152] VIDARIS	18 yrs & older	No of URTs per person	18 months	Vit D3 & Placebo	100,000IU	3.7	161	RR =0.97	0.85,1.11	0.65	A
					Placebo	3.7	161	1	**Reference**		
		No. of days if missed work per episode*			100,000IU	0.76	161	RR 1.03	0.81, 1.30	0.82	
					Placebo	0.76	161	RR 1	**Reference**		
		Duration of symptoms			100,000IU	12	161	RR 0.96	0.73, 1.25	0.76	
					Placebo	12	161	RR 1	**Reference**		

Table 31d. Vitamin D and immunologic outcomes: Results of infectious disease RCTs (dichotomous outcomes) (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Intervention	No. of Events	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Goldring 2013[161]		wheeze ever	3 yrs	Vit D	either 800 IU ergocalciferol daily or 200,000 IU calciferol (single dose)	11	56	OR 0.56	0.20, 1.57	0.27	A
					control	14	50	OR 1.00	**Reference**		
		lower respiratory tract infection			either 800 IU ergocalciferol daily or 200,000 IU calciferol (single dose)	14	54	OR 1.00	0.35, 2.91	1	
					control	11	50	OR 1.00	**Reference**		

*Included in Table 31d (dichotomous outcomes) because differences reported as relative risks.

Vitamin D and Pregnancy-Related Outcomes

This section includes preeclampsia, small-for-gestational age, and preterm birth.

Preeclampsia

Synopsis

For the current report, two RCTs, two prospective studies, and five nested case control studies were identified that assessed the outcome of risk for preeclampsia. The RCTs, whose results were combined and reported in one article, found that supplementation with 2000IU or 4000IU vitamin D per day decreased the risk for preeclampsia. Both prospective studies observed an association between second-trimester serum 25(OH)D concentrations and decreased risk for preeclampsia. Three of the five nested case control studies observed an association between low 25(OH)D concentrations (<50nmol/L) and preeclampsia or severe preeclampsia.

In the original report, a single nested case-control study found an association between low 25(OH)D concentration (<37.5 nmol/L) early in pregnancy and preeclampsia. The study was rated B for methodological quality.

Detailed Presentation (Tables 32a-c & 33a-c)

In the current report, two RCTs, whose results were combined and reported in one article, found that supplementation with 2000IU or 4000IU vitamin D per day decreased the risk for preeclampsia.

The U.S. NICHD and Thrasher trials randomized 504 women to receive 0, 2000, or 4000IU vitamin D per day in addition to their prenatal vitamins. Supplementation with 4000IU increased serum 25(OH)D concentrations and resulted in a trend toward lower rates of preeclampsia; increasing maternal serum 25(OH)D concentrations were strongly associated with decreased risk for preeclampsia (OR 0.77, 95% CI 0.57, 1.06) (rated B).[42]

Two prospective cohort studies observed an inverse association between second-trimester serum 25(OH)D concentrations and risk for preeclampsia. One Chinese study that followed 697 women found that low serum 25(OH)D at 12 to 18 weeks gestation and 24 to 26 weeks gestation was associated with a higher risk for preeclampsia ($p<0.05$) (rated B).[172] A U.S. study that followed a cohort of 1,141 pregnant women in Camden NJ found that serum 25(OH)D less than 50nmol/L at study entry (13.7±5.7 weeks gestation) was associated with an increased risk for preeclampsia (OR 2.86, 95% CI 1.28, 6.41) (rated B).[173]

Five nested case control studies assessed the association between maternal serum 25(OH)D concentrations during early or mid-gestation and the risk for subsequent preeclampsia. Three of these studies observed an association between maternal 25(OH)D concentrations and subsequent risk for preeclampsia. One Canadian study of 1,301 women (cases and controls) found that the risk for preeclampsia was increased for women with low 25(OH)D concentrations (<50nmol/L vs. ≥50nmol/L) during the second trimester but not during the first trimester.[174] A U.S. study of 51 women diagnosed with preeclampsia and 204 matched controls (in a cohort of 3,992 women) that divided midgestational 25(OH)D status into tertiles found that low serum 25(OH)D concentrations (<37.5 nmol/L) was associated with severe preeclampsia.[175] A U.S. study aimed at identifying placental growth

factors that, combined with 25(OH)D concentrations, would predict the risk for preeclampsia found that low maternal 25(OH)D concentrations, by itself, had some predictive power regarding the risk for preeclampsia.[176] Two additional nested case control studies, the Canadian EMMA study and a U.S. study found that low first trimester maternal 25(OH)D levels were not associated with risk for preeclampsia.[177,178]

In the original report, a nested case-control study evaluated the association between 25(OH)D concentration and risk of preeclampsia.[179] The study found an association between 25(OH)D concentrations less than 37.5 nmol/L (measured approximately 30 wk before outcome assessment) and increased risk of preeclampsia**.** The study was rated B for methodological quality.

Findings by Life Stage

- **0–6 mo**
  No data
- **7 mo–2 y**
  Not applicable
- **3–8 y**
  Not applicable
- **9–18 y**
  Not applicable
- **19–50 y**
  See pregnant and lactating women.
- **51–70 y**
  Not applicable
- **≥71 y**
  Not applicable
- **Postmenopause**
  Not applicable
- **Pregnant & lactating women**
  For the current report, one RCT reported that higher dose vitamin D supplementation decreased the risk for preeclampsia. Two prospective cohort studies and three nested case control studies found an association between low 25(OH)D concentrations at mid-gestation and the risk for preeclampsia, and two nested case control studies found no association with first trimester 25(OH)D concentrations and risk for preeclampsia. In the original report, a single nested case-control study found an association between low 25(OH)D concentration (<37.5 nmol/L) early in pregnancy and preeclampsia.

Other Outcomes

Synopsis

In the current report, we identified two cohort studies that assessed the association between maternal serum 25(OH)D concentrations and the risk for giving birth to a small-for-gestational-age (SGA) infant and one cohort study and one nested case control study that assessed the association with preterm birth. One of the two cohort studies found an increase in the risk for SGA at the lowest concentration range of maternal serum 25(OH)D

compared with higher serum vitamin D concentrations among both white and black women; the other study observed a U-shaped association between serum 25(OH)D and the risk for risk for SGA among white women. The prospective study observed an increase in the risk for preterm birth among women carrying twins whose serum 25(OH)D was less than 75nmol/L. The nested case control study that assessed the association with preterm birth found no significant association.

We found no studies for the current report on the relationship of maternal serum 25(OH)D and pregnancy hypertension.

The original report did not identify any eligible studies on the relationship of vitamin D with or without calcium and high blood pressure, preterm birth, or small-for-gestational-age infants.

Detailed Presentation (Tables 32a-c & 33a-c)

In the current report, two cohort studies assessed the association between maternal serum 25(OH)D concentrations and the risk for giving birth to a SGA infant and one nested case control study that assessed the association with preterm birth.

One U.S. cohort study of 1,067 white and 236 black mother-infant pairs found an association of serum 25(OH)D less than 25nmol/L with an increased risk for SGA, compared with serum 25(OH)D of 25nmol/L or greater (adjusted OR 3.94 [1,51, 10.29]). When the data were further adjusted for race, the adjusted odds ratio fell slightly (3.17 [1.16, 8.63]).[45]

The other cohort study, which assessed 412 mother-infant pairs, found a U-shaped association between serum 25(OH)D and risk for SGA among white mothers. The lowest risk was observed from 60 to 80 nmol/L; compared with serum 25(OH)D 37.5–75 nmol/L, SGA odds ratios (95% CI) for levels,37.5 and.75 nmol/L were 7.5 (1.8, 31.9) and 2.1 (1.2, 3.8), respectively. This association was not seen among black mothers (study rated A). [180]

A multisite U.S. prospective study of 211 twin pregnancies found that late second trimester serum 25(OH)D concentrations of 75nmol/L or greater were associated with a decreased risk for preterm birth (aOR 0.40, 95%CI 0.2, 0.8) (rated A).[181] One Canadian nested case control study of 227 mother infant pairs, the EMMA study, found no association of low maternal serum 25(OH)D (<37.5nmol/L) at 10 to 21 weeks gestation with the risk for preterm birth.[177]

Findings by Life Stage

- **0–6 mo**
  No data
- **7 mo–2 y**
  Not applicable
- **3–8 y**
  Not applicable
- **9–18 y**
  Not applicable
- **19–50 y**
  See pregnant and lactating women.
- **51–70 y**
  Not applicable

- **≥71 y**
  Not applicable
- **Postmenopause**
  Not applicable
- **Pregnant & lactating women**
  In the current report, we identified two cohort studies that assessed the association between maternal serum 25(OH)D concentrations and the risk for giving birth to a small-for-gestational-age (SGA) infant and one nested case control study that assessed the association with preterm birth. The two cohort studies found an increase in the risk for SGA at the lowest concentration range of maternal serum 25(OH)D compared with higher serum vitamin D concentrations. One study found this increase in risk for both white and black mothers, whereas the other study found that the risk increased only for white mothers. A prospective study observed an increase in the risk for preterm birth among women carrying twins whose serum 25(OH)D was less than 75nmol/L at mid-gestation. A nested case control study that assessed the association of serum 25(OH)D with preterm birth found no significant association. We found no studies for the current report on the relationship of maternal serum 25(OH)D and pregnancy hypertension.

Table 32a. Vitamin D and preeclampsia: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted					
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Bodnar 2007[179] PEPPS[A] US (41°N) [17535985]	• Health status • Age range, y • Male (%)	Healthy 20–29 0%	• Assay method • Season blood drawn	ELISA ND	Comparison of mean 25(OH)D levels in cases and controls		x	x			
NEW Studies											
Wei, 2012[174] International Trial of Antioxidants in the Prevention of Preeclampsia (INTAPP) Canada	• Health status • Mean age (SD), y • Male (%)	31.3% in high-risk group including chronic hypertension, prepregnancy diabetes, multiple pregnancy, or a history of preeclampsia 30.3 (4.8) 0%			Preeclampsia stratified by 25(OH)D tertiles		X	X	X	X	X
Shand, 2010[177] EMMA Vancouver, Canada	• Health status • Mean age (SD), y • Male (%)	nd nd 0%			Preeclampsia stratified by 25(OH)D medians	X	X	X		X	X
Baker, 2010[175] US Chapel Hill, NC	• Health status • Mean age (range), y • Male (%)	Healthy 28 (23–34) 0%			Severe preeclampsia stratified by 25(OH)D tertiles		X	X		X	
Powe, 2010[178] US Boston, MA	• Health status • Mean age (SD), y • Male (%)	nd 30.4 (SD 6) 0%			Severe preeclampsia stratified by 25(OH)D quartiles		X			X	

Table 32a. Vitamin D and preeclampsia: Characteristics of observational studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Woodham 2011[176] Chapel Hill, UK	• Health status • Mean age (range), y • Male (%)	nd 29 (25–33) 0%		Severe preeclampsia stratified by 25(OH)D		X	X		X	
Scholl 2013[173] Camden Study Camden, New Jersey US	• Health status • Mean age (SD), y • Male (%)	Healthy/NR 22.8 (SD 5.4) 0%		Preeclampsia stratified by 25(OH)D quartiles	X	X	X			X
Wei 2013[172] INTAPP Canada	• Health status • Mean age (SD), y • Male (%)	nd 28.68 (SD 5.44) 0%		Preeclampsia stratified by 25(OH)D medians		X	X		X	X

[A]Pregnancy Exposures and Preeclampsia Prevention Study

Table 32b. Vitamin D and other pregnancy outcomes: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
NEW Studies										
Baker 2011[182]	Health status	Healthy		Preterm birth 25(OH)D tertiles		X	X		X	
	Mean age (Range), y	33 (30–37)								
	Male (%)	0								
Bodnar, 2010[180] US Pittsburgh, PA (latitude 40 degree N)	• Health status	Healthy		Small-for-gestational age births stratified by 25(OH)D tertiles		X	X			X
	• Mean age (Range), y	21 (14–35)								
	• Male (%)	0%								
Burris 2012[45] US, Massachusetts	• Health status	nd		Small-for-gestational age births stratified by 25(OH)D tertiles		X	X		X	
	• Mean age (SD), y	33 (SD 4.5)								
	• Male (%)	0%								
2013[181] US	• Health status	nd NR		Preterm birth at less than 35 wk and Preterm birth at less than 32 wk stratified by 25(OH)D sextiles		X	X		X	X
	• Mean age (SD), y									
	• Male (%)	0%								

Table 32c. Vitamin D and preeclampsia: Characteristics of RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
				Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
NEW Studies									
Wagner 2013[42] US	• Health status • Mean age (Range), y • Male (%)	nd 27 (18–41) 0%	Preeclampsia stratified by 25(OH)D tertiles		X				

Table 33a. Vitamin D and preeclampsia: Results of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	Study Quality
Bodnar 2007[179A] PEPPS[B] US (41°N) [17535985]	Pregnancy	Preeclampsia (55/1198; 4%)[C]	ND	25(OH)D[D]	<37.5 (vs. >37.5)	49	265	5	1.7, 14.1	B
NEW Studies										
Wei 2012[174]		preeclampsia	12–18 weeks gestation	25(OH)D	per SD increase	32	697	0.79	0.52, 1.20	A
					<50	15	272	1.24	0.58, 2.67	
					>50	17	425	1.00	**Reference**	
			24–26 weeks gestation		per SD increase	28	604	0.68	0.44, 1.05	
					<50	19	236	3.24	1.37, 7.69	
					>50	9	368	1.00	**Reference**	
Shand 2010[177]		preeclampsia	10–20 weeks gestation	25(OH)D	<37.5	10	NR	0.91	0.31, 2.62	A
					≥37.5	18	NR	1.00	**Reference**	
					<50	17	NR	1.39	0.54, 3.53	
					≥50	11	NR	1.00	**Reference**	
					<75	21	NR	0.57	0.19, 1.66	
					≥75	6	NR	1.00	**Reference**	
Baker 2010[175]	Pregnant or lactating women	severe preeclampsia	NR	25(OH)D	< 50	22	160	5.41	2.02, 14.52	B
					50–74.9	10	51	2.16	0.85, 5.40	
					≥75	11	30	1.00	**Reference**	

Table 33a. Vitamin D and preeclampsia: Results of observational studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	Study Quality
Powe 2010[178]		severe preeclampsia	NR	25(OH)D	Quartile 1 (ND)	39 (overall)	170 (overall)	1.50	0.57, 3.96	B
					Quartile 2 (ND)			1.04	0.39, 2.76	
					Quartile 3 (ND)			0.67	0.23, 1.91	
					Quartile 4 (ND)			1.00	**Reference**	
Scholl 2013[173] Camden Study		preeclampsia	20 weeks gestation	25(OH)D	<30	12	121	2.13	1.07, 4.26	B
					30–40	12	116	2.09	1.04, 4.22	
					40–50	7	154	0.94	0.41, 2.17	
					>=50	38	750	1.00	**Reference**	
Wei 2013[172] INTAPP		preeclampsia	24–26 weeks gestation	25(OH)D	<50 nmol/L	NR	NR	2.97	1.23, 7.20	B
					>=50 nmol/L			1.00	**Reference**	
Woodham 2011[176]		severe preeclampsia	NR	25(OH)D		41	164	0.95	0.94, 0.97	B

[A] This is a nested case-control study.
[B] Pregnancy Exposures and Preeclampsia Prevention Study.
[C] Incidence obtained from the "parent" cohort study in which this case control study is nested.
[D] Early in pregnancy, approximately 30 wk. before outcome assessment.

Table 33b. Vitamin D and other pregnancy outcomes: Results of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	Study Quality
Baker 2011[182]		preterm birth	NR	25(OH)D	<50 nmol/L	3	11	0.82	0.19, 3.57	A
					50–74.9 nmol/L	8	32	0.87	0.34, 2.25	
					≥75 nmol/L	29	117	1.00	Reference	
Bodnar 2010[180] white women	Pregnant or lactating women	Small-for-gestational age births	NR	25(OH)D	<37.5 nmol/L	8	11	7.5	1.8, 31.9	A
					37.5–75 nmol/L	27	134	1.0	**Reference**	
					>75 nmol/L	42	128	2.1	1.2, 3.8	
black women		Small-for-gestational age births	NR	25(OH)D	<37.5 nmol/L	17	65	1.5	0.6, 3.5	
					37.5–75 nmol/L	13	63	1.0	**Reference**	
					>75 nmol/L	4	11	2.2	0.5, 9.0	
Bodnar 2013[181]		preterm birth at less than 35 wk	24–28 weeks gestation	25(OH)D	< 75	42	85	1.0	**Reference**	A
					>=75	33	126	0.4	0.2, 0.8	
					per 1-SD increase	75	211	0.5	0.3, 0.8	
					Q1 (median 43.6)	27	52	1.0	**Reference**	
					Q2 (median 72.7)	24	53	1.0	0.4, 2.5	
					Q3 (median 95.4)	15	53	0.4	0.2, 1.1	
					Q4 (median 116)	9	53	0.2	0.1, 0.7	
		preterm birth at less than 32 wk			< 75	16	85	1.0	**Reference**	
					>=75	9	126	0.2	0.1, 0.6	
					per 1-SD increase	25	211	0.4	0.2, 0.8	
					Q1 (median 43.6)	10	52	1.0	**Reference**	
					Q2 (median 72.7)	7	53	0.5	0.1, 1.7	
					Q3 (median 95.4)	6	53	0.4	0.1, 1.5	
					Q4 (median 116)	2	53	0.1	0.02, 0.7	

Table 33c. Vitamin D and preeclampsia: results of RCTs (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration	Intervention	No. of Events	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Wagner 2013[42]		Preeclampsia	NR	2000 IU	9	201	RR 0.55	0.22, 1.34	0.43	B
				4000 IU	4	193	RR 0.25	0.08, 0.80	0.05	
				control	9	110	RR 1.00	**Reference**		

Vitamin D and Clinical Outcomes of Bone Health

The current report sought RCTs and observational studies reporting on the association between vitamin D intervention or exposure and clinical outcomes related to bone health, including rickets, fractures, muscle strength, and falls, published since the original report.

For bone health outcomes**, the original report** (e.g., bone mineral density, fracture, fall or muscle strength) relied on a recent comprehensive systematic review (Effectiveness and Safety of Vitamin D in Relation to Bone Health) performed by the Ottawa EPC (Table 28).[8] Because the Ottawa's EPC report did not report separate analyses for the effect of vitamin D supplementation alone, the results for the effect of vitamin D alone or in combination with calcium supplementation were presented in the "Combined Vitamin D and Calcium" section. The Ottawa EPC report also did not report separate analyses by study designs (i.e., RCTs, prospective cohorts, before and after study, and case-control studies), although the report primarily included RCTs.

The Ottawa EPC report was updated with literature published between January 2006 and September 2008, selected according to our eligibility criteria. Only RCTs qualified for inclusion.

Rickets

Synopsis

No new studies assessing the association between vitamin D intervention or exposure and the risk for rickets met the inclusion criteria for the current report.

The Ottawa EPC report concluded that there is fair evidence for an association between low serum 25(OH)D concentrations and confirmed rickets, regardless of the types of assay measures of 25(OH)D concentrations (RIA, CPBA, HPLC). According to the report, there is inconsistent evidence to determine whether there is a threshold concentration of serum 25(OH)D above which rickets do not occur.

Our updated search did not identify new RCTs examining the effect of vitamin D supplementation on rickets.

Detailed Presentation (Table 34)

Ottawa EPC Report: Rickets—infants (0 through 12 months) and young children (1 through 5 years)

Overall, there is fair evidence for an association between low serum 25(OH)D concentrations and confirmed rickets, regardless of the types of assay measures of 25(OH)D concentrations (RIA, CPBA, HPLC). There is inconsistent evidence to determine whether there is a threshold concentration of serum 25(OH)D above which rickets do not occur.

Six studies (one RCT, three before-after and two case-control studies) reported mean or median serum 25(OH)D concentrations < 30 nmol/L in children with rickets whereas the other studies reports the mean or median 25(OH)D concentrations were above 30 nmol/L (and up to 50 nmol/L). In seven of eight case-control studies, serum 25(OH)D concentrations were lower in the children with rickets compared with controls.

Findings by Life Stage

- **0–6 mo**
  The Ottawa EPC report included infants and young children and concluded that there is fair evidence for an association between low serum 25(OH)D concentrations and confirmed rickets, regardless of the types of assay measures of 25(OH)D concentrations (RIA, CPBA, HPLC). There were no new data since the Ottawa EPC report.
- **7 mo–2 y**
  The Ottawa EPC report included infants and young children. There were no new data since the Ottawa EPC report.
- **3–8 y**
  The Ottawa EPC report included young children. There were no new data since the Ottawa EPC report.
- **9–18 y**
  Not reviewed
- **19–50 y**
  Not reviewed
- **51–70 y**
  Not reviewed
- **≥71 y**
  Not reviewed
- **Postmenopause**
  Not reviewed
- **Pregnant & lactating women**
  Not reviewed

Table 34. Summary of systematic review of the effect of vitamin D on bone health (not updated from original report)

Author Year [PMID]	Cranney 2007[8] [18088161]
Design	Systematic review of RCTs and observational studies
Population	• Include all ages • Exclude secondary causes of osteoporosis (e.g., glucocorticoid-induced, renal or liver disease) • Exclude studies on the treatment of vitamin D-dependent rickets (to minimize clinical heterogeneity as treatments is often nondietary sources of vitamin D)
Intervention (Exposure) and Comparator	Intervention (Exposure): • Include vitamin D_2 or D_3 with or without calcium. • Exclude vitamin D preparations, calcitriol, α-calcidol (because they are not nutritional supplements, and have different safety profile) Comparator: • No vitamin D or lower doses/levels of vitamin D
Results	See text for summary results for the following outcomes in both vitamin D and combined vitamin D and calcium sections of the report: • Rickets • Fractures, falls, or performance measures • Bone mineral density or bone mineral contents • How does dietary intake of vitamin D from fortified foods and vitamin D supplementation affect serum 25(OH)D Concentrations • Adverse events
Comments	Case-control studies were included but always summarized separately from cohort studies and RCTs. Meta-analyses were performed to pool results from RCTs only.

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	Yes
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	No	**Publication bias assessed?**	No
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes		

Fractures, Falls, or Performance Measures

Synopsis

The current report did not identify any new trials that assessed the effect of interventions of vitamin D alone on fracture risk; eight observational studies assessed the association between serum 25(OH)D and fracture risk; (interventions that assessed the effect of vitamin D and calcium are described in Table 59 and the accompanying text). We identified two RCTs that examined the effect of supplementation with vitamin D on the risk for falls, and two RCTs on muscle strength; four prospective cohort studies assessed the association between serum(OH)D concentrations and muscle strength, and one prospective cohort study assessed the association between serum 2(OH)D and falls. The RCTs reported significant effects of vitamin D supplementation on decreasing risk for falls and increasing muscle strength. Three of the four prospective cohort studies reported associations between lower serum 25(OH)D and decreased or decreasing muscle strength and performance; the fourth saw no association. An association was seen between lower 25(OH)D concentrations and increased risk for falls. The studies are described in detail below.

Overall, the Ottawa EPC report, **summarized in the original report**, concluded that the associations between serum 25(OH)D concentrations and the risk of fractures, falls, and performance measures among postmenopausal women or elderly men are inconsistent.[8]

Findings from three additional RCTs (published after the Ottawa EPC report)[183-185] also did not show significant effects of either vitamin D_2 or D_3 supplementation (daily doses ranged from 400 IU to 822 IU) in reducing the risk of total fractures or falls in elderly populations (≥71 years old).

Detailed Presentation (Tables 35a-d & 36a-d)

RCTs of Vitamin D Supplementation Identified for the Current Report that Assessed the Effects on Falls and Muscle Strength

Two RCTs were identified for the current report that examined the effects of vitamin D supplementation on the risk for falls among older adults (both rated A). A 1-year study of 242 adults in Germany,70 to 91 years of age (average age 77, 75% women) randomized the group to receive 800IU vitamin D and 1000mg calcium daily or calcium and placebo alone; the vitamin D group had a significant decrease in the number of first fallers (OR 0.73 [0.54, 0.96]).[186] A 1-year study of 382 postmenopausal Australian women, 70 to 90 years of age randomized the women to receive 1000IU vitamin D_2 and 1000mg calcium daily or placebos; supplemented women had a significantly decreased risk of falling especially in winter and a decreased risk for first falls but not for two or more falls.[187]

Two RCTs were identified for the current report that examined the effects of 1 year of vitamin D supplementation on muscle strength (both rated A). The two studies assessed the effect of supplementation with vitamin D and calcium (compared with calcium alone) on strength in older adults. A 1-year study of 242 adults in Germany,70 to 91 years of age (average age 77, 75% women) randomized the group to receive 800IU vitamin D and 1000mg calcium daily or calcium and placebo alone; the vitamin D group had significant improvements in muscle strength and in timed up and go.[186] A study of 261 community dwelling, vitamin D insufficient, Australian women, 70 to 90 years of age, were randomized to 1,000IU vitamin D and 1000 mg calcium daily or calcium alone: only women with the lowest baseline muscle strength had significant improvements.[188]

Observational Studies of Muscle Strength and Risk for Falls

Four prospective cohort studies were identified for the current report that assessed the association between serum 25(OHD) concentrations and muscle strength or loss among older adults. Among a subset of the WHI cohort serum 25(OH)D concentrations of 75nmol/L or more were associated with higher muscle strength and performance scores at 6 years' followup (study rated A).[189] The Rancho Bernardo Study, which followed a cohort of 1,065 men and women of average age 74.6 over 2.5 years found that lower serum 25(OH)D concentrations were associated with declining muscle function in women but not in men (rated C).[190]A study of 646 men and women in Tasmania, average age 62, over 2.6 years, found that serum 25(OH)D concentrations of 50nmol/L or less were associated lower muscle strength at followup (rated B).[191]The Health ABC Study followed 2,641 men and women, ages 70 to 80, over 4 years and found that lower serum 25(OH)D concentrations were not associated with a faster rate of decline in muscle strength over time (rated B).[192]

The one cohort study that assessed the association between serum 25(OH)D and risk for falls followed 463 men and women, 70 to 90 years of age over 1 year and found that serum 25(OH)D of 50nmol/L or less was associated with an increased risk for falls (rated B).[193]

Observational Studies of Fracture Prevention Identified for the Current Report

Eight prospective cohort and nested case control studies that assessed the association between vitamin D exposure and fracture risk were identified that met the inclusion criteria for the current study.

Hip fracture risk was assessed in five studies that ranged in followup from a median of 6.4 years to an average of 11 years. The Cardiovascular Health Study, a prospective cohort study that followed 1,621older community dwelling adults over 11 years and found a small but significant increase in hip fracture risk for those with the lowest serum levels of 25(OH)D (rated A).[87] The Health ABC study, which followed a population of 2,501 older adults for a median of 6.4 years, found no significant association of 25(OH)D exposure and risk for hip fracture (rated B).[194] A reassessment of a subgroup of women in the WHI Observational Study (OS) found an association of low vitamin D and increased risk for hip fracture (rated B).[195] A study that assessed the risk for hip and other osteoporotic fracture among 4,749 NHANES III participants ages 65 and over found that among those followed for less than 10 years, serum 25(OH)D was a significant predictor for hip and other major osteoporotic fracture; however at 10 years or more, the association was no longer significant (rated A).[196] The NOREPOS study followed a cohort of 21,774 men and women 65 to 79 years of age for 10.7 years and observed that low serum 25(OH)D (less than 42.2 nmol/L) predicted a 38 percent increased risk for hip fracture in this population (95% CI 9, 74) compared with a 25(OH)D concentration of 67.9 nmol/L or more (rated A).[197] Nonvertebral fracture risk was assessed in two studies (both with B ratings). One nested case control study of the MrOS study population of older men found no association between low serum 25(OH)D alone and nonvertebral fracture risk.[198] The Health ABC cohort study found no significant association of serum 25(OH)D with nonvertebral fracture risk.[194]

Total fragility fracture was assessed in two studies. A reassessment of WHI OS data after 8.6 years follow up found an association of lower serum 25(OH)D concentrations with a significantly increased fracture risk for white women but a much smaller association for black women, no association for Hispanic or native American women, and an association of higher 25(OH)D concentrations with higher risk for fragility fracture in Asian American women (results of the WHI CaD trial are discussed later in the section on vitamin D and calcium supplementation).[199] The CEOR study, a study of postmenopausal Saudi women with a follow up of 5.2 years, observed that low vitamin D was an independent predictor of increased risk for osteoporotic fracture.[200]

Ottawa EPC Report: Fractures—Postmenopausal Women or Elderly Men

Overall, there is inconsistent evidence for an association between serum 25(OH)D concentrations and the risk of fractures. Fifteen studies (three prospective cohorts and twelve case-controls) reported on the association between serum 25(OH)D concentrations and fracture rates. One of three cohorts reported an inverse association between serum 25(OH)D concentrations and fracture rates, and nine of twelve case-control studies found significantly lower 25(OH)D concentrations in cases versus controls. Differences in results may be attributed to whether all relevant confounders were controlled for and differences in baseline serum 25(OH)D concentrations. Other factors may also contribute to the heterogeneity, such as diagnosis of fractures.

Ottawa EPC Report: Falls—Postmenopausal Women or Elderly Men

Overall, there is fair evidence of an association between lower serum 25(OH)D concentrations and an increased risk of falls in institutionalized elderly. One study suggested a serum 25(OH)D concentration below 39 nmol/L was associated with an increased risk of falls.

Five studies (one RCT, three cohorts and one case-control) evaluated the association between serum 25(OH)D concentrations and risk of falls. One RCT, two of the three cohorts and one case-control study reported an inverse association between serum 25(OH)D concentrations and a risk of falls. In one cohort with a low percentage of vitamin D deficient participants, the association did not persist after adjustment for age and illness severity. In another cohort with an undetermined proportion of vitamin D deficient participants no significant association between serum 25(OH)D concentrations and risk of falls was observed. One case-control study reported no significant association between serum 25(OH)D concentrations and risk of falls after adjusting for serum PTH.

Ottawa EPC Report: Performance Measures—Postmenopausal Women or Elderly Men

Overall, there is inconsistent evidence for an association of serum 25(OH)D concentrations with performance measures. In studies that reported an association, specific concentrations below which, declines in performance measures were increased, ranged from 50 to 87 nmol/L.

Seven studies (three RCTs and four cohorts) assessed the relation between 25(OH)D concentrations and performance related measures. Two of the three RCTs and two of the four cohorts reported an association between 25(OH)D concentrations and performance measures. The other studies did not find an association between 25(OH)D concentrations and performance measures.

Additional RCTs Published After the Ottawa EPC Report

We identified three additional RCTs (published after the Ottawa EPC report)[183-185] that examined the effect of either vitamin D_2 or D_3 supplementation on total fractures, falls, or performance in elderly populations (≥71 years old). All three RCTs were rated C. In two of the three RCTs[183,184] calcium supplementation (800 or 1200 mg/d) was given to all participants. Baseline serum 25(OH)D concentrations were less than 40 nmol/L. The other RCT did not provide any information on background calcium intake or baseline serum 25(OH)D concentrations.[185] All three RCTs reported no significant reduction in the risk of total fracture or falls in elderly populations at daily vitamin D doses ranging from 400 IU to 822 IU.[183-185] Only one of the three new RCTs among elderly reported data on performance measures. Vitamin D supplementation (400 IU/d) improved gait speed and body sway in healthy elderly subjects.[183]

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  A single RCT identified for the current report reported no significant effect of

vitamin D supplementation of 12 to 14-year old girls on muscle strength, in spite of improved serum status. Not reviewed **in the original report**

- **19–50 y**
  No data
- **51–70 y**
  The Ottawa EPC report concluded that the associations between serum 25(OH)D concentrations and risk of fractures, falls, and performance measures are inconsistent. There were no new data since the Ottawa report
- **≥71 y**
  Two of three trials identified for the current report that assessed the effects of vitamin D_2 or D_3 supplementation on the risk for falling among men and women 70 and older reported a significant decrease in the risk for some categories of falls. Two trials identified for the current report that assessed the effects of vitamin D_2 or D_3 supplementation on muscle strength reported some improvement but this finding was limited to those with lowest baseline strength in one study. Analysis of elderly adults in two large prospective cohort studies found a strong inverse association between serum 25(OH)D and risk for hip fracture and major osteoporotic fracture; however one of the studies observed the association only at followup times of 10 years or less. In the original report, findings from three new RCTs did not show significant effects of either vitamin D_2 or D_3 supplementation (daily doses ranged from 400 IU to 822 IU) in reducing the risk of total fractures or falls among men and women in this life stage.
- **Postmenopause**
  Of two trials identified for the current report that assessed the effects of vitamin D_2 or D_3 supplementation on the risk for falling among postmenopausal women 70 and older, one reported a significant decrease in the risk for some categories of falls, and one reported no effect. **This trial reported improved muscle strength among postmenopausal women 70 and older but only in those with lowest baseline strength.** The Ottawa EPC report concluded that the associations between serum 25(OH)D concentrations and risk of fractures, falls, and performance measures are inconsistent. There were no new data since the Ottawa report **identified for the original report.**
- **Pregnant & lactating women**
  Not reviewed

Table 35a. Vitamin D and bone health: Characteristics of RCTs published after the Ottawa EPC report (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Lyons 2007[185] South Wales, UK (52°N) [17473911]	• Health status	Living in care facilities including some elderly with mobility, cognitive, visual, hearing or communication impairments	nd	Vit D_2 100,000 IU 4-monthly vs. placebo	80% (percentage of occasions observed to take tablets)	
	• Mean age (range), y	84 (62–107)				
	• Male (%)	23.7				
Burleigh 2007[184] Scotland (55° 57'N) [17656420]	• Health status	Inpatient with high levels of comorbidity, mortality and polypharmacy	25(OH)D: 22.0 nmol/L	Vit D_3 800 IU/d + Ca carbonate 1200 mg/d vs. Ca carbonate 1200 mg	Ca group=87%, Vit D+Ca group=89% (total study drug taken/total study drug prescribed, as recorded in drug prescription charts)	
	• Mean age (SD), y	83 (7.6)				
	• Male (%)	40				
Bunout 2006[183] Chile (32°S) [16797903]	• Health status	Healthy	25(OH)D: ≤40 nmol/L	Ca 800 mg/d vs. Ca 800 mg/d + Vit D 400 IU/d (with and without exercise training)	92% (tablet counting)	
	• Mean age (SD), y	76 (4)				
	• Male (%)	11.6				
NEW Studies						
Pfeifer, 2009[186] Bad Pyrmont, Germany Graz, Austria	• Health status	Healthy	25(OH)D: 22.0 nmol/L	1000mg and 800 IU daily vs. 1000mg daily	>80% (noncompliant participants excluded)	
	• Mean age (SD), y	77 (SD 4)				
	• Male (%)	26%				
Prince, 2008[187] Perth, Australia	• Health status	Vitamin d deficient/depleted	25(OH)D: ≤40 nmol/L	1000mg of Ca & 1000 IU of Vit D2 daily vs. 1000mg of Ca & placebo daily	92% (tablet counting)	
	• Mean age (SD), y	77.4 (5) Range: 0–90				
	• Male (%)	0%				

Table 35b. Vitamin D and muscle strength: Characteristics of RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
NEW Studies						
Lips, 2010[201] Multiple countries; North America(9 centers); Europe (3 centers)	• Health status • Mean age (SD), y • Male (%)	nd 77.6 (SD 6.6) nd	serum vitamin D- placebo- 35.3+/-13.8 nmol/l, D3- 34.25+/-11.0 nmol/l serum calcium- placebo- 9.4+/- 0.4mg/dl, D3- 9.4+/- 0.4mg/dl	Double placebo vs. 60,000 IU/week Vs. 500mg/twice daily & 60,000 IU/week	All completes were adherent	
Pfeifer, 2009[186] Bad Pyrmont, Germany Graz, Austria	• Health status • Mean age (SD), y • Male (%)	Healthy 77 (SD 4) 26%	Serum vitamin D level:55±18 nmol/L Calcium intake: 608±38 mg/d	1000 mg & 800 IU daily Vs. 1000 mg daily	>80% (noncompliant participants excluded)	
Ward, 2010[202] Manchester, UK	• Health status • Mean age (SD), y • Male (%)	Healthy 13.8 (SD 0.7) Range: 12–14 11.6	total serum 25OHD placebo: 17.9 ± 7.4 nmol/l vit D group: 18.1 ± 8.0 nmol/l	150,000 IU/ quarterly Vs. Placebo	100%	
Zhu, 2010[188] Perth, Australia	• Health status • Mean age (SD), y • Male (%)	plasma 25(OH)D concentration less than 60 nmol/L 77 (SD 4.8) 0%	Serum 25(OH)D 17.7 ±10.5 nmol/L	1,000 mg/d Ca +1,00 IU vit D2 Vs. 1,000 mg/d Ca	vitamin D group: 86.7% control group: 86.8%	

Table 35c. Vitamin D and muscle strength: Characteristics of prospective cohorts (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
NEW Studies						
Dam, 2009[190] Rancho Bernardo study California, US	• Health status • Mean age (SD), y • Male (%)	nd 74.6 (SD 10.3) 38%	serum vitamin D: men-107.6±29.2 nmol/L, women-100.8±33.1 nmol/L	10–80 nmol/l 82.5–97.5 nmol/l 100–112.5 nmol/l 115–337.5 nmol/l Vs. 10–90 nmol/l 92.5–102.5 nmol/l 105–120 nmol/l 122.5–262.5 nmol/l	nd	
Houston, 2012[192] Healthy, Aging and Body Composition US Pittsburgh, Memphis	• Health status • Mean age (SD), y • Male (%)	diabetes, cvd, copd, knee pain 74.7 (SD 2.9) 49%	1/3–25(OH)D <50nmol/L, 2/3–<75nmol/L	<50 nmol/L Vs. 50–<75 nmol/L Vs. ≥75 nmol/L	nd	
Menant, 2012[193] Sydney, Australia	• Health status • Mean age (SD), y • Male (%)	Healthy 78 (SD 4.6) Range: 70–90 46%	Serum vitamin D–62.2±24.6 nmol/L	≤ 50nmol/l Vs. > 50nmol/l	nd	
Scott, 2010[191] Tasmanian Older Adult Cohort Study (TASOAC) Tasmania, Australia	• Health status • Mean age (SD), y • Male (%)	plasma 25(OH)D concentration less than 60 nmol/L 62 (SD 7) Range: 50–79 51%	Serum 25OH(D) Low vitamin D: 37.1±8.4 High vitamin D: 67.8±13.4	> 50nmol/l Vs. ≤ 50nmol/l	nd	

Table 35d. Vitamin D and bone health: Characteristics of observational studies published after the Ottawa EPC report (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
NEW Studies						
de Boer 2012[87] Cardiovascular Health Study US (various)	• Health status • Mean age (SD), y • Male (%)	nd 74.6 (SD 4.6) 30%	Serum vitamin D: 66.2+/-25.8 nmol/L	Normal level Vs. Low level (season specific, ranges 43–61 nmol/L)	nd	
Barbour, 2012[194] US Pittsburgh, PA and Memphis, TN	• Health status • Mean age (SD), y • Male (%)	nd nd nd	Dietary calcium intake, median (IQR) (mg/d) 717 (515–973) 736 (532–995) 719 (517–978) 716 (501–940) Supplemental calcium intake (% yes) 18.3 25.0 17.4 28.7 Supplemental vitamin D intake (% yes) 8.3 13.1 8.1 12.2 in order of groups: hip fracture no/yes, any non-spine fracture no/yes	Quartile 1: ≤44.5 nmol/l vs. Quartile 2: 44.5–60.9 nmol/L vs. Quartile 3: 60.9–79.9 nmol/L vs. Quartile 4: >79.9 nmol/L	nd	
Barrett-Connor, 2012[198] US (various)	• Health status • Mean age (SD), y • Male (%)	Healthy, Overweight/Obese, and diabetes = 10%; mild CKD (GFR<60 mL/min/1.73m3) =12% 74 (SD 6) 100%	nd	Normal level Vs. Low vit D	nd	

Table 35d. Vitamin D and bone health: Characteristics of observational studies published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Burgi 2011[203] US	• Health status • Mean age (SD), y • Male (%)	nd 19.5 (SD 1.8) 0%	nd	3.8–49.3 nmol/L vs. 49.3–66.5 nmol/L vs. 66.5–82.0 nmol/L vs. 82.0–99.5 nmol/L vs. 99.5–281.3 nmol/L	Nd
Cauley 2011[199] WHI OS US	• Health status • Mean age (Range), y • Male (%)	nd 64 (50–70) nd	nd	<50 nmol/L vs. 50–<75 nmol/Ll vs. ≥75 nmol/L	nd
Michael, 2011[189] US (various)	• Health status • Mean age (SD), y • Male (%)	nd 70.3 (SD 3.7) Range: 50–79 0%	Serum vitamin D- 48.2+/-21.4 nmol/L	≥ 75 nmol/l Vs. 50–74nmol/l Vs. 25–49 nmol/l Vs. ≤ 25 nmol/l	nd
Rouzi 2012[200] Jeddah, Saudi Arabia	• Health status • Mean age (SD), y • Male (%)	Healthy 61.3 (SD 7.2) nd	Serum 25(OH)D: 34.27±22.80 nmol/L	<17.90 nmol/L vs. >45.1 nmol/L	nd
Cauley, 2008[195] WHI-OS nd	• Health status • Mean age (Range), y • Male (%)	Post-menopausal Nd (50–79) 0%	Serum 25(OH)D controls: 59.60 ± 18.05 nmol/l cases: 55.95 ± 20.28 nmol/l	Quartile 1: 9.2–47.5 nmol/L vs. Quartile 2: 47.6–70.6 nmol/L vs. Quartile 3: 60.2–70.6 nmol/L vs. Quartile 4: 70.7–121.5 nmol/L vs. per 2.5 nmol/L decrease vs. per 25 nmol/L decrease	nd
Looker 2013[196] NHANES III US (multiple cities)	• Health status • Mean age (SD), y • Male (%)	NR 75.2 25.7%	osteoporotic fracture- yes: 57.5 nmol/L, no: 60.1 nmol/L hip fracture- yes: 57.6 nmol/L, 60.0 nmol/L	3 categories per 1 SD unit decline in serum 25OHD	nd

Table 35d. Vitamin D and bone health: Characteristics of observational studies published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Menant, 2012[193] Sydney, Australia	• Health status • Mean age (SD), y • Male (%)	nd 78 (SD 4.6) Range: 70–90 46%	serum vitamin D- 62.2±24.6 nmol/L	≤ 50nmol/l Vs. > 50nmol/l	nd
Michael, 2011[189] US (various)	• Health status • Mean age (SD), y • Male (%)	nd 70.3 (SD 3.7) Range: 50–79 0%	Serum vitamin D- 48.2+/-21.4 nmol/L	≥ 75 nmol/l Vs. 50–74nmol/l Vs. 25–49 nmol/l Vs. ≤ 25 nmol/l	nd
Holvik 2013[197] Norwegian Epidemiologic Osteoporosis Studies (NOREPOS) Norway	• Health status • Mean age (SD), y • Male (%)	46.1–59.2% good or very good health 71.9 (SD 3.9) 28%	median (25th and 75th percentiles) s-25(OH)D in the randomly sampled subcohort was 53.5 (42.2, 67.8) nmol/L	Quartile 1: 4.5–42.1 vs. Quartile 2: 42.2–53.5 vs. Quartile 3: 53.5–67.8 vs. Quartile 4: 67.9–250.0	nd

Table 36a. Vitamin D and bone health: Results of RCTs published after the Ottawa EPC report (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Lyons 2007[185] [17473911]	≥71 both sexes	First fracture	1°	Median time to first fracture = 387 (IQR: 220–582) d in Vit D_2 group; 367 (IQR:139–618) d in placebo group	Vit D_2 ~822 IU[A]	205	1670	HR Vit D/placebo	0.95	0.79, 1.15	NS	C
					Placebo	218	1673					
Burleigh 2007[184] [17656420]	≥71 both sexes	Fall	1°	Median 1 (IQR 15–71 d)	Vit D_3 800 IU + Ca carbonate 1200 mg	36	100	RR (Vit D+Ca)/Ca	0.82	0.59, 1.16	NS	C
					Ca carbonate 1200 mg	45	103					
		Fracture	1°	Median 1 (IQR 15–71 d)	Vit D_3 800 IU + Ca carbonate 1200 mg	1	100	nd	nd		NS	
					Ca carbonate 1200 mg	3	103					
Bunout 2006[183] [16797903]	≥71 both sexes	Fall	2°	9 mo	Ca 800 mg	13[B]	24	Fall free survival curve	nd		NS	C
					Ca 800 mg + exercise training	6[B]	22					
					Vit D 400 IU + Ca 800 mg	9[B]	24					
					Vit D 400 IU + Ca 800 mg + Exercise training	8[B]	22					

Table 36a. Vitamin D and bone health: Results of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
NEW Studies												
Pfeifer, 2009[186] Multiple Countries		Primary–Falls (≥1)	1°	12 mo	1000 mg & 800 IU daily	NR	122	RR	0.73	0.54, 0.96	<0.01	A
					1000 mg daily	NR	120	RR	1.00	**Reference**		
Prince, 2008[187] Perth, Australia		Primary–Falls (≥1)	1°	1 y	1000mg of Ca & 1000 IU of Vit D2 daily	80	151	OR	0.66 0.61	0.41, 1.06 0.37, 0.99 adjusted for height	NS < 0.05	A
					1000mg of Ca & placebo daily	95	151	OR	1.00	**Reference**		
		Primary–1 fall			1000mg of Ca & 1000 IU of Vit D2 daily	32	151	OR	0.50	0.28, 0.88	< 0.05	
					1000mg of Ca & placebo daily	51	151	OR	1.00	**Reference**		
		Primary–Falls (≥2)			1000mg of Ca & 1000 IU of Vit D2 daily	NR	151	OR	0.86	0.50, 1.49	> 0.05	
					1000mg of Ca & placebo daily	NR	151	OR	1.00	**Reference**		
		Primary–First fall in winter/spring			1000mg of Ca & 1000 IU of Vit D2 daily	38	151	OR	0.55	0.32, 0.96	< 0.05	
					1000mg of Ca & placebo daily	54	151	OR	1.00	**Reference**		
		Primary–First fall in summer/autumn			1000mg of Ca & 1000 IU of Vit D2 daily	42	151	OR	0.81	0.46, 1.42	> 0.05	
					1000mg of Ca & placebo daily	41	151	OR	1.00	**Reference**		

Note: Outcomes cells are shaded for the Control rows.
[A] Daily dose was calculated from the intermittent doses that were used in the study (i.e., 100,000 IU tablets every 4 months)
[B] Estimated from figure

Table 36b. Vitamin D and muscle strength: Results of RCTs (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Lips, 2010[201] Multiple countries; North America(9 centers); Europe (3 centers)	71+	Short physical performance battery (SPPB) summary score	2°	16 wk	8,400 IU/weekly	109		9.00	change= 0.355	0.108, 0.601	-0.25	-0.60, -0.10	0.17	A
					Placebo	104		9.07	change= 0.601	0.351, 0.852	Reference	NR		
		Short physical performance battery (SPPB) gait speed			8,400 IU/weekly	109	cm/s	93.70	change= 3.10	-0.252, 6.458	-0.84	-5.63, 3.95	0.73	
					Placebo	104	cm/s	88.70	change= 3.94	0.567, 7.38	Reference	NR		
Pfeifer, 2009[186] Bad Pyrmont, Germany Graz, Austria	71+	Secondary-Quadriceps strength left leg	2°	12 mo	1000 mg & 800 IU daily	114	Newton	211.00	final= 236	SD=75	+12	-8.6, 32.6	0.25	A
					1000 mg daily	114	Newton	217.00	final= 224	SD=83	Reference			
		Secondary-Body sway total length			1000 mg & 800 IU daily	114	mm	86.00	final= 81	SD=32	-5	-13, 3	0.22	
					1000 mg daily	114	mm	90.00	final= 86	SD=30	Reference			
		Secondary-Timed up and go (TUG)			1000 mg & 800 IU daily	114	secs	9.00	final= 7.5	SD=3.4	-0.8	-1.9, 0.3	0.16	
					1000 mg daily	114	secs	8.50	final= 8.3	SD=5.1	Reference			

Table 36b. Vitamin D and muscle strength: Results of RCTs (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Ward, 2010[202] Manchester, UK	9–18 yrs	Maximum force	1°	1 yr	150,000 IU/ quarterly	33	kN/kg	2.80	change= -0.08	SD=0.22	-0.04	-0.12, 0.04	0.32	A
					Placebo	32	kN/kg	2.71	change= -0.04	SD=0.04	Reference			
		Eslinger fitness index			150,000 IU/ quarterly	33	Per-cent	89.44	change= -4.31	SD=9.32	+0.17	-3.8, 4.2	0.93	
					Placebo	32	percent	85.41	change= -4.48	SD=6.68	Reference			
		Efficiency			150,000 IU/ quarterly	33	Per-cent	87.76	change= 2.72	SD=8.57	+1.10	-0.91, 3.12	0.10	
					Placebo	32	Per-cent	84.36	change= -0.56	SD=7.42	Reference			
		Velocity			150,000 IU/ quarterly	33	m/sec	2.19	change= 0.02	SD=0.13	+0.03	-0.03, 0.09	0.28	
					Placebo	32	m/sec	2.12	change= -0.01	SD=0.09	Reference			
		Jump height			150,000 IU/ quarterly	33	m	0.34	change= 0.01	SD=0.04	+0.01	-0.01, 0.03	0.32	
					Placebo	32	m	0.33	change= 0.00	SD=0.04	Reference			
		Maximum power relative to body weight			150,000 IU/ quarterly	33	kW/kg	39.52	change= -1.06	SD=4.18	+0.18	-1.6, 2.0	0.84	
					Placebo	32	kW/kg	37.81	change= -1.24	SD=2.91	Reference			
		Spine bone mineral content (BMC)			150,000 IU/ quarterly	35	g	11.73	change= 0.52	SD=0.39	-0.05	-0.24, 0.15	0.62	
					Placebo	33	g	11.97	change= 0.57	SD=0.43	Reference			
		Tibia 66% cortical bone mineral content (Ct BMC)			150,000 IU/ quarterly	33	mg/ mm	268.38	change= 7.68	SD=12.26	-1.98	-8.4, 4.4	0.54	
					Placebo	31	mg/ mm	261.23	change= 9.66	SD=13.38	Reference			

Table 36b. Vitamin D and muscle strength: Results of RCTs (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Zhu, 2010[188] Perth, Australia	71+	Timed up and go (TUAG)	1°	1y	1,000 mg/d Ca +1,00 IU vit D2	129	secs	11.0	Final=8.1	SD=3.9	-0.9	-2.2, 0.5	0.2	A
					1,000 mg/d Ca	132	secs	10.8	Final=9	SD=7	Reference			
		lower limb muscle strength: ankle dorsiflexion			1,000 mg/d Ca +1,00 IU vit D2	129	kg	11.6	Final=10.9	SD=3.7	0	-0.9, 0.9	1	
					1,000 mg/d Ca	132	kg	11.8	Final=10.9	SD=4	Reference			
		lower limb muscle strength: knee flexor			1,000 mg/d Ca +1,00 IU vit D2	129	kg	11.8	Final=12.9	SD=3.5	-0.1	-1.0, 0.8	0.83	
					1,000 mg/d Ca	132	kg	11.9	Final=13	SD=3.9	Reference			
		lower limb muscle strength: knee extensor			1,000 mg/d Ca +1,00 IU vit D2	129	kg	18.3	Final=18	SD=5	-0.3	-1.6, 1.0	0.65	
					1,000 mg/d Ca	132	kg	18.8	Final=18.3	SD=5.5	Reference			
		lower limb muscle strength: hip extensor			1,000 mg/d Ca +1,00 IU vit D2	129	kg	14.6	Final=17.2	SD=5.2	+0.3	-1.1, 1.7	0.67	
					1,000 mg/d Ca	132	kg	14.4	Final=16.9	SD=6.2	Reference			
		lower limb muscle strength: hip abductor			1,000 mg/d Ca +1,00 IU vit D2	129	kg	12.3	Final=14.5	SD=4.1	+0.4	-0.7, 1.5	0.48	
					1,000 mg/d Ca	132	kg	12.2	Final=14.1	SD=4.9	Reference			
		lower limb muscle strength: hip flexor			1,000 mg/d Ca +1,00 IU vit D2	129	kg	14.5	Final=15.4	SD=4.2	0	-1.1, 1.1	1	
					1,000 mg/d Ca	132	kg	14.5	Final=15.4	SD=4.8	Reference			
		lower limb muscle strength: hip adductor			1,000 mg/d Ca +1,00 IU vit D2	129	kg	14.4	Final=16.4	SD=4.2	+0.1	-1.1, 1.3	0.86	
					1,000 mg/d Ca	132	kg	14.7	Final=16.3	SD=5.2	Reference			

Table 36c. Vitamin D and muscle strength: Results of prospective cohorts (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Concentration, nmol/L	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Dam, 2009[190] Rancho Bernardo study California, US		Change in grip strength (women)	2°	2.5 y (median)	10–80 nmol/l	159	kg (%)	NR	Change= -0.78	-4.76, 6.32	+1.55	NC	0.22	C
					82.5–97.5 nmol/l	181			Change= -3.30	-1.34, 7.95	+5.63	NC		
					100–112.5 nmol/l	153			Change= -2.01	-6.85, 2.83	+0.32	NC		
					115–337.5 nmol/l	163			**Change= -2.33**	-7.10, 2.45	**Reference**	**Reference**		
		Change in grip strength (men)			10–90 nmol/l	114			Change= -0.71	-2.12, 3.54	+1.63	NC	0.22	
					92.5–102.5 nmol/l	86			Change= -0.64	-3.91, 2.63	+1.7	NC		
					105–120 nmol/l	110			Change= -0.37	-2.34, 3.07	+1.97	NC		
					122.5–262.5 nmol/l	99			**Change= -2.34**	-5.15, 0.48	**Reference**	**Reference**		
		Change in Timed up and go (TUG)(women)			10–80 nmol/l	159			Change= 21.92	16.22, 27.62**	+13.79	NC	0.002	
					82.5–97.5 nmol/l	181			Change= 7.37	2.69, 12.04	-0.76	NC		
					100–112.5 nmol/l	153			Change= 8.48	3.48, 13.48	+0.35	NC		
					115–337.5 nmol/l	163			**Change= 8.13**	3.16, 13.10	**Reference**	**Reference**		
		Change in Timed up and go (TUG) (men)			10–90 nmol/l	114			Change= 3.36	-1.11, 7.82	+1.94	NC	0.99	
					92.5–102.5 nmol/l	86			Change= 3.52	-1.75, 8.79	+2.1	NC		
					105–120 nmol/l	110			Change= 4.95	0.69, 9.21	+3.53	NC		
					122.5–262.5 nmol/l	99			**Change= 1.42**	-3.05, 5.09	**Reference**	**Reference**		
		Change in Timed chair stands (TCS)(women)			10–80 nmol/l	159			Change= 21.98	16.28, 27.67**	+14.28	NC	0.002	
					82.5–97.5 nmol/l	181			Change= 7.38	2.70, 12.06	-0.32	NC		
					100–112.5 nmol/l	153			Change= 8.51	3.51, 13.51	+0.81	NC		
					115–337.5 nmol/l	163			**Change= 7.70**	2.58, 12.62	**Reference**	**Reference**		

Table 36c. Vitamin D and muscle strength: Results of prospective cohorts (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Concentration, nmol/L	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
		Change in Timed chair stands (TCS)(men)			10–90 nmol/l	114			Change= 3.36	-1.11, 7.82	+1.94	NC	0.99	
					92.5–102.5 nmol/l	86			Change= 3.52	-1.75, 8.79	+2.1	NC		
					105–120 nmol/l	110			Change= 4.95	0.69, 9.21	+3.53	NC		
					122.5–262.5 nmol/l	99			**Change= 1.42**	-3.05, 5.09	**Reference**	**Reference**		
Houston, 2012[192] Healthy, Aging and Body Composition US Pittsburgh, Memphis		knee extensor strength	1°	4y	<50 nmol/L	1818	nm/ kg	12.83	Final=11.9	SE=0.2	NC	NC	0.76	B
					50–<75 nmol/L			13.01	Final=11.9	SE=0.2				
					≥75 nmol/L			12.91	Final=11.8	SE=0.2				
		grip strength			<50 nmol/L	1971	kg	28.87	Final=29.2	SE=0.4	NC	NC	0.09	
					50–<75 nmol/L			29.71	Final=29.8	SE=0.4				
					≥75 nmol/L			29.81	Final=30.0	SE=0.4				

Table 36c. Vitamin D and muscle strength: Results of prospective cohorts (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Concentration, nmol/L	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Menant, 2012[193] Sydney, Australia		Primary-Grip strength	1°	1 y	> 50 nmol/l	309	kg	NR	final= 28.7	SD=11.7	+4.7	3.3, 6.1	<0.001	B
					≤ 50nmol/l	154	kg		final= 24.0	SD=10.3	**Reference**			
		Primary-Quadriceps strength			> 50 nmol/l	309	kg		final= 28.9	SD=11.9	+6	5, 7	<0.001	
					≤ 50nmol/l	154	kg		final= 22.9	SD=10.4	**Reference**			
		Primary-Finger press reaction time			> 50 nmol/l	309	ms		final= 235.4	SD=45.2	-11.7	NR	<0.001	
					≤ 50nmol/l	154	ms		final= 247.1	SD=50.0	**Reference**			
		Primary-Sway, eyes open-floor			> 50 nmol/l	309	mm2		final= 76.5	SD=40.1	-5.4	-11.0, 0.2	0.06	
					≤ 50nmol/l	154	mm2		final= 81.9	SD=46.0	**Reference**			
		Primary-Sway, eyes open-foam			> 50 nmol/l	309	mm2		final= 182.2	SD=97.5	-5.6	-17.7, 6.5	0.37	
					≤ 50nmol/l	154	mm2		final= 187.8	SD=89.9	**Reference**			
		Primary-Physiological Profile assessment (PPA) fall risk score			> 50 nmol/l	309			final= 0.8	SD=0.9	-0.2	-0.3, -0.1	<0.001	
					≤ 50nmol/l	154			final= 1.0	SD=0.9	**Reference**			
		Primary-Maximal balance range			> 50 nmol/l	309	mm		final= 155.7	SD=56.8	+21.1	14.2, 28.0	<0.001	
					≤ 50nmol/l	154	mm		final= 134.6	SD=49.7	**Reference**			
		Primary-Coordinated stability score			> 50 nmol/l	309			final= 13.6	SD=12.4	-5.0	-7, -3	<0.001	
					≤ 50nmol/l	154			final= 18.6	SD=13.3	**Reference**			
		Primary-Choice stepping reaction time			> 50 nmol/l	309	secs		final= 987.4	SD=215.1	-73.4	-101.7, -45.1	<0.001	
					≤ 50nmol/l	154	secs		final= 1060.8	SD=223.0	**Reference**			
		Primary-6 m walk speed			> 50 nmol/l	309	m/s		final= 0.73	SD=0.16	+0.06	0.04, 0.08	<0.001	
					≤ 50nmol/l	154	m/s		final= 0.67	SD=0.17	**Reference**			

Table 36c. Vitamin D and muscle strength: Results of prospective cohorts (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Concentration, nmol/L	No. Analyzed	Unit	Baseline	Change/ Final	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Scott, 2010[191] Tasmanian Older Adult Cohort Study (TASOAC) Tasmania, Australia		Appendicular lean mass	1°	2.6 y	> 50nmol/l	389	percent	62.20	NR	NR	+0.01	-0.52, 0.54	0.963	B
					≤ 50nmol/l	297	percent	59.30	NR	NR	**Reference**			
		Leg strength			> 50nmol/l	389	kg	100.80	NR	NR	+5.74	0.65, 10.82	0.027	
					≤ 50nmol/l	297	kg	91.50	NR	NR	**Reference**			
		Leg muscle quality			> 50nmol/l	389	kg/kg	5.90	NR	NR	+0.49	0.17, 0.82	0.003	
					≤ 50nmol/l	297	kg/kg	5.50	NR	NR	**Reference**			

Table 36d. Vitamin D and bone health: Results of observational studies published after the Ottawa EPC report (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Concentration, nmol/L	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
de Boer 2012[87] Cardiovascular Health Study US (various)		Hip fracture	1°	11 yrs	Normal level	118	1126	HR	1.00	Reference	NR	A
					Low level (season specific, ranges 43–61 nmol/L)	72	495		1.34	0.97, 1.84		
Barbour, 2012[194] US Pittsburgh, PA and Memphis, TN	age 70–79	Hip fracture	1°	2 yrs	Quartile 1: ≤44.5 nmol/L	84	2501	HR	1.92	0.97, 3.83	0.217	B
					Quartile 2: 44.5–60.9 nmol/L				0.75	0.32, 1.72		
					Quartile 3: 60.9–79.9 nmol/l				1.86	1.00, 3.45		
					Quartile 4: >79.9 nmol/l				1.00	**Reference**		
		nonspine fracture	1°	2 yrs	Quartile 1: ≤44.5 nmol/L	247	2494	HR	1.21	0.83, 1.75	0.752	
					Quartile 2: 44.5–60.9 nmol/L				1.01	0.68, 1.49		
					Quartile 3: 60.9–79.9 nmol/l				1.12	0.78, 1.60		
					Quartile 4: >79.9 nmol/l				1.00	**Reference**		
Barrett-Connor, 2012[198] US (various)	51–70 yrs; ≥71 yrs	nonspine fracture	1°	4.6 yrs	Normal level	100	594	HR	1.2	0.8, 1.8		A
					Low vit D	34	183		1.00	**Reference**		
Burgi 2011[203] US	9–50 yrs	stress fracture	1°	NR	3.75–49.25 nmol/L	600	1200	OR	1.00	**Reference**	0.02	B
					49.5–66.5 nmol/L				0.77	0.54, 1.11		
					66.8–82 nmol/L				0.76	0.52, 1.10		
					82.3–99.5 nmol/L				0.61	0.42, 0.91		
					99.75–281.25 nmol/L				0.51	0.34, 0.78		

Table 36d. Vitamin D and bone health: Results of observational studies published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Concentration, nmol/L	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Cauley 2011[199] WHI OS US	Post-meno-pausal women	fractures	1°	8.6 yrs								
whites					<50 nmol/L	150	270	OR	1.00	**Reference**	0.02	A
					50– <75 nmol/L	156	321		0.82	0.58, 1.16		
					≥75 nmol/L	84	189		0.56	0.35, 0.90		
blacks					<50 nmol/L	241	508	OR	1.00	**Reference**	0.043	
					50– <75 nmol/L	108	193		1.48	1.05, 2.10		
					≥75 nmol/L	30	57		1.33	0.73, 2.43		
Hispanics					<50 nmol/L	89	182	OR	1.00	**Reference**	0.72	
					50– <75 nmol/L	71	140		1.02	0.69, 1.79		
					≥75 nmol/L	31	60		1.09	0.50, 2.37		
Asians					<50 nmol/L	37	80	OR	1.00	**Reference**	0.22	
					50– <75 nmol/L	45	85		1.49	0.76, 2.93		
					≥75 nmol/L	30	59		1.66	0.68, 4.02		
native Americans					<50 nmol/L	29	55	OR	1.00	**Reference**	0.29	
					50– <75 nmol/L	9	18		0.64	0.15, 2.79		
					≥75 nmol/L	6	15		0.43	0.09, 2.08		
Rouzi, 2012[200] Jeddah, Saudi Arabia		fragility fractures	1°	5.2 yrs	<17.90 nmol/L	138	707	OR	1.25	0.91, 1.70		A
					>45.1 nmol/L				1.00	**Reference**		
Cauley, 2008[195] WHI-OS nd		hip fractures	1°	7.1 yrs	Quartile 1: 9.2–47.5 nmol/L	NR	244	OR	1.71	1.05, 2.79		A
					Quartile 2: 47.6–70.6 nmol/L	NR	195		1.09	0.70, 1.71		
					Quartile 3: 60.2–70.6 nmol/L	NR	167		0.82	0.51, 1.31		
					Quartile 4: 70.7–121.5 nmol/L	NR	193		1.00	**Reference**		
					per 2.5 nmol/L decrease	NR	799		1.03	1.01, 1.05	0.015	
					per 25 nmol/L decrease	NR	799		1.33	1.06, 1.68		
Looker 2013[196] NHANES III		major osteoporotic fracture	1°	7 yrs	per 1 SD unit decline in serum 25OHD	400	4749	RR	1.27	1.12, 1.44		A
						212	NR		1.14	0.97, 1.34		
						188	NR		1.40	1.13, 1.74		

Table 36d. Vitamin D and bone health: Results of observational studies published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Concentration, nmol/L	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Holvik 2013[197] Norwegian Epidemiologic Osteoporosis Studies (NOREPOS)		hip fracture	1°	10.7 yrs	Q1: 4.5–42.1	317	256	HR	1.34	1.05, 1.70		A
					Q2: 42.2–53.5	294	255		1.13	0.90, 1.44		
					Q3: 53.5–67.8	272	255		1.10	0.87, 1.39		
					Q4: 67.9–250.0	279	256		1.00	**Reference**		
Menant, 2012[193] Sydney, Australia		Primary-Falls in men	1°	1 y	≤ 50nmol/l	94	215	IRR	1.93	1.19, 3.15	0.008	B
					> 50nmol/l			IRR	1.00	**Reference**		
		Primary-Falls in women			≤ 50nmol/l	115	248	IRR	0.83	0.56, 1.23	0.362	
					> 50nmol/l			IRR	1.00	**Reference**		
Michael, 2011[189] US (various)		Primary-Physical performance summary score	1°	6 y	≥ 75 nmol/l	NR	64	RR	3.66	1.88, 5.45	<0.001	A
					50–74nmol/l	NR	148	RR	2.32	0.89, 3.75		
					25–49 nmol/l	NR	255	RR	1.64	0.28, 3.01		
					≤ 25 nmol/l	NR	67	RR	1	**Reference**		

Vitamin D and All-Cause Mortality

Synopsis

The current report identified 25 cohort studies that assessed the association between serum 25(OH)D concentration and risk for all-cause mortality. Of the 25, seven found no association (rated 1A, 6B), 16 found an association of lower 25(OH)D concentrations with increased risk for mortality (rated 6A, 9B: one article reported on two studies), and two reported an association of both higher and lower 25(OH)D concentrations with increased mortality risk (rated A and B).

The assessment of the literature on vitamin D and all-cause mortality in the original report was based on a reanalysis of a systematic review of RCTs on vitamin D supplementation for mortality.[i] In addition, it summarizes four observational studies on the association of vitamin D and all-cause mortality.

Three RCTs from the previous systematic review and an additional C rated RCT were included in our reanalysis. Three used daily doses that ranged between 400 and 880 IU, and one used 100,000 IU every 3 months. Our meta-analysis of the 4 RCTs (13,833 participants) shows absence of significant effects of vitamin D supplementation on all-cause mortality (RR = 0.97, 95% CI: 0.92, 1.02; random effects model). There is little evidence for between-study heterogeneity in these analyses.

One cohort study (rated B for methodological quality) found a significant trend for lower odds for death with increasing 25(OH)D concentrations. Three other cohort studies did not find a significant association between 25(OH)D concentrations and all-cause mortality. These three studies were rated C for their methodological quality.

The above are applicable to older (50–70 y) and elderly (≥71 y) men and women (mean age was >70 y in the included studies).

Detailed Presentation (Tables 37, 38, & 39)

The current report identified 25 observational studies that assessed the association between serum 25(OH)D concentrations and all-cause mortality as an outcome. None of the outcomes fit the criteria needed to be included in the meta-analysis that was conducted for the original report and are described below. As mentioned in the Methods section, **the original report** updated and reanalyzed published meta-analyses of mortality outcomes. That report drew its own conclusions based on its analyses. The original report also commented on the concordance of its conclusions with those of the published meta-analyses.

Relevant Published Systematic Reviews of RCTs (With Meta-Analyses)

The original report identified two systematic reviews (with meta-analyses) of RCTs that summarized the effect of vitamin D supplementation with or without calcium on mortality.[204,205] One systematic review (Avenell 2008) examined only trials on fall prevention, and briefly described results on mortality.[205] The second meta-analysis (Autier 2007) focused specifically on mortality.[204] It included all RCTs identified in the first, as well as additional trials (which were

[i] Numerical data were extracted from previous systematic reviews—no additional studies were identified. For this reason, we did not appraise studies for their methodological quality.

not eligible for the primary analysis of the Avenell 2008 systematic review, namely prevention of falls).[204] Therefore, the Autier 2007 meta-analysis was used as the basis for our reanalysis.

Table 37 summarizes the findings of the Autier 2007 systematic review.

Table 37. Summary of systematic review on vitamin D supplementation and all-cause mortality (not updated from original report)

Author Year [PMID]	Autier 2007[204] [17846391]
Design (Search Years)	Randomized controlled trials (1992–2006)
Population	Community dwelling or institutionalized adults
Intervention (Exposure) and Comparator	Supplementary vitamin D (at least 1000 mg/d) without calcium vs. placebo or no treatment
Results	18 trials of combined vitamin D and vitamin D + calcium RR: 0.93 (95% CI 0.87, 0.99); favoring vitamin D (± calcium) supplementation Statistically homogeneous In our reanalysis we and excluded 3 of 18 trials and separated studies with vitamin D only from those with vitamin D and calcium combination. For details and results of our reanalysis, see text.
Comments	See text in vitamin D and vitamin D + calcium sections for reanalyses of the separated trials. Study participants, vitamin D assays, and vitamin D status are not described in detail.

AMSTAR Criteria			
A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	No	**Study quality appropriately used in analysis?**	NA
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	No	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes	The meta-analysis did not perform quality assessment (neither using individual quality items nor using quality scores)	

Additional Identified RCTs (Not Included in Published Systematic Reviews)

No RCTs were identified for the current report that assessed the effect of vitamin D or vitamin D and calcium supplementation on risk for all-cause mortality. For the original report, Lyons 2007 (n=3343, 24% males) used monthly supplementation with 100,000 IU of vitamin D_2, orally for 3 years.[185] The trial took place in South Wales (latitude ~52°N) and included older people (mean age 84 y) living in sheltered accommodation. The primary outcome was prevention of fractures. The Lyons 2007 RCT received grade "C" for the all-cause mortality outcome, because of inconsistencies in the reported data. This RCT is included in the reanalysis described below.

Reanalysis

For the re-analysis conducted in the original report, they excluded 5 of 18 trials in the Autier 2007 meta-analysis: One trial was on patients with congestive heart failure,[206] one was published only in abstract form,[207] in one trial the controls also received supplementation with vitamin D, albeit with a smaller dose,[208] and two trials used vitamin D injections.[209,210] One additional eligible RCT (Lyons 2007)[185] was identified and included in our meta-analysis.

Overall, four trials (13,899 patients) used only vitamin D supplementation without calcium. Among the four trials, sample sizes ranged from 2578 to 5292 participants. Followup periods ranged from 36 to 60 months. Vitamin D doses in most trials ranged between 400 and 830 IU per day.

Overall, there were no significant effects of vitamin D supplementation on mortality. The RR was 0.97 (95% CI 0.92, 1.02), with no evidence for between-study heterogeneity (P=0.39, I^2=0%).

Cohort Studies

The current report identified 25 cohort studies (one article reported on two studies, and one study was reported in two articles) that assessed the association between serum 25(OH)D concentration and risk for all-cause mortality. Of the 25, six found no association (rated 1 rated A, 6 rated B).[58,70,77,79,83,98,144] These studies ranged in length of followup from 3 to 24 years. Sixteen found an association of lower 25(OH)D concentrations with increased risk for mortality (6 rated A, 9 rated B: one article reported on two studies);[60,73-77,81,86,87,101,211-218] most associations were small, limited to a particular subgroup, or limited to the first 3 years after baseline measurement.[211] Two studies reported an association of both higher and lower 25(OH)D concentrations with increased mortality risk, that is a j-shaped association (rated A and B).[84,218] A 15-year followup assessment of 15,099 NHANES participants (age 20 and older) reported the lowest association with all-cause mortality at a 25(OH)D concentration of 81 nmol/L. For 25(OH)D concentrations less than 20nmol/L, the RR for all-cause mortality was 2.2 (95% CI 1.6, 2.9) and for 25(OH)D concentrations greater than 120nmol/L, the RR was 1.5 (95% CI 1.02, 2.30).[218] These same associations were seen for both men and women, for adults 20 to 64 years of age and for non-Hispanic whites.

The original report identified four prospective cohort studies described in 5 publications.[85,219-222] The characteristics of the four cohorts are shown in **Table 38**. One was rated "B"[219] for methodological quality and the remaining were rated "C."

Table 39 summarizes the findings of the four studies. Briefly, only Jia 2007[219] found a statistically significant trend between increasing 25(OH)D concentrations and lower odds for all-cause mortality (P=0.03). However, none of the odds ratios of the different 25(OH)D categories was significant, and if anything, they suggest an U shaped relationship between 25(OH)D and mortality. All other cohorts did not find significant associations. Melamed 2008[85] performed analyses in subgroups of men and women, and <65 or ≥65 years of age, and found no significant associations (Table 33).

Findings by Life Stage

- **0–6 mo**
  No data
- **7 mo–2 y**
  No data
- **3–8 y**
  No data
- **9–18 y**
  No data
- **19–50 y**
  A 15-year followup analysis of NHANES III data identified for the current report observed a j-shaped association of serum 25(OH)D concentrations with all-cause mortality for adults 20 to 64 years of age, with serum concentrations less than 30 nmol/L and greater than 120nmol/L associated with a higher risk. A subgroup

analysis of people younger than 65 years in NHANES III **identified for the original report** (Melamed 2008) found no significant associations between 25(OH)D concentrations and all-cause mortality.

- **51–70 y**
  The current report identified one study that observed a significant association of serum 25(OH)D concentrations and all-cause mortality among adults 50 to 74 years of age. Overall, there were no significant effects of vitamin D supplementation on mortality.
    - In a random effects model meta-analysis of five RCTs (n=13,899) the summary RR was 0.97 (95% CI 0.92, 1.02), with no evidence for between-study heterogeneity (p=0.39, I^2=0%). The mean participant age was more than 70 years in these RCTs.
    - Overall, data from four cohorts suggest no association between baseline 25(OH)D measurements and all-cause mortality (one cohort found a statistically significant trend for). A subgroup analysis of people aged 65 years or older in NHANES III (Melamed 2008) found no significant associations between 25(OH)D concentrations and all-cause mortality.
- **≥71 y**
  Of three cohort studies identified for the current report that assessed the association between serum 25(OH)D and all-cause mortality, one in men who were 85 years old at baseline, one in individuals 70 to 88 years old followed up to 9.2 years, and the third in individuals who were 77 years old at baseline, one reported no association and two observed an association between lower serum 25(OH)D concentrations and increased all-cause mortality. For studies identified for the original report, the above (51–70 y) are applicable.
- **Postmenopause**
  No data
- **Pregnant & lactating women**
  No data

Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted					
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Jia 2007[219] UK (57°N) [17442130]	• Health status • Age range, y • Male (%)	Not terminally ill or demented >75 52	• Assay method • Season blood drawn	RIA ND	Comparison of various 25(OH)D concentration categories		X		X	X	X
Sambrook 2004 & 2006[220,221] FREE[A] Australia (33°S) [15531500 & 16598375]	• Health status • Age range, y • Male (%)	Not bedridden >65 22	• Assay method • Season blood drawn	RIA (Dia-sorin) ND	Association with log 25(OH)D		X		X		
Visser 2006[222] Longitudinal Aging Study Netherlands (52°N) [16960177]	• Health status • Age range, y • Male (%)	General population[B] >65 51	• Assay method • Season blood drawn	Competitive protein binding ND	Comparison of various 25(OH)D concentration categories		X	X			X
Melamed 2008[85] NHANES III US (various) [18695076]	• Health status • Age mean (range), y • Male (%)	General population 45 (≥20) 46	• Assay method • Season blood drawn	RIA (Dia-sorin) ND	Comparison of various 25(OH)D concentration categories	X	X	X	X	X	X
NEW Studies											
Bolland 2010[58] New Zealand	• Health status • Age range, y • Male (%)	Healthy Post-menopausal 74 (SD 4.2) 0%			Comparison of various 25(OH)D concentration categories		X	X	X		X
Cawthon 2010[98] MrOS (multisite) US	• Health status • Mean age (Age range), y • Male (%)	>80% Excellent/good health status 74 (> or =65) nd			Association with log 25(OH)D	X	X	X	X	X	X

Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
de Boer 2012[87] Cardiovascular Health Study US (various)	• Health status • Mean Age (SD), y • Male (%)	nd 74 (SD 4.6) 30%		Comparison of various 25(OH)D concentration categories		X	X	X		X
Eaton 2011[70] WHI substudy US (multisite)	• Health status • Mean Age (SD), y • Male (%)	nd 65.1 (SD 7.6) 0%		Post-menopausal women 50–79 years stratified by 25(OH)D quartiles			X	X	X	X
Fedirko 2012[101] EPIC US (4 sites)	• Health status • Mean Age (SD), y • Male (%)	nd 62.1 (4.2) 40.5%		Diagnosis at age of 62 stratified by 25(OH)D quintiles		X	X	X	X	X
Hutchinson 2010[79] Tromsø Study Tromso, Norway	• Health status • Mean Age (range), y • Male (%)	Nd nd nd		Smoking and non-smoking cause of death stratified by 25(OH)D quartiles		X	X	X		X
Jacobs 2011[144] Women's Healthy Eating and Living Well (WHEL) Study	• Health status • Mean Age (SD), y • Male (%)	Cancer in remission 51.9 (SD 9) 0%		Breast cancer survivors stratified by 25(OH)D concentration categories						
Johansson 2012[211] MrOS Sweden: Gothenburg, Malmö, Uppsala	• Health status • Mean Age (SD), y • Male (%)	Some with diabetes, htn, cancer, stroke, MI, angina 75.7 (SD 3.4) 100%		Death and mortality stratified by varying 25(OH)D concentration levels		X		X		X
Kestenbaum 2011[81] Cardiovascular Health Study US (various)	• Health status • Mean Age (range), y • Male (%)	nd 73 (SD 4) 42%		All-cause mortality stratified by 25(OH)D quartiles						

Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Kritchevsky 2012[212] Health, Aging, and Body Composition (ABC) Study US Pittsburgh, Memphis	• Health status • Mean Age (SD), y • Male (%)	Well-functioning 74.7 (SD 2.9) 49%		All-cause mortality stratified by 25(OH)D quartiles		X	X	X	X	X
Lin 2012[83] General Population Trial of Linxian, China	• Health status • Mean Age (SD), y • Male (%)	Healthy, Hypertension 56.5 (7.9) 55%		All-cause mortality stratified by continuous 25(OH)D		X	X	X		X
Michaelsson 2010[84] Uppsala Longitudinal Study of Adult Men Uppsala, Sweden	• Health status • Mean Age (range), y • Male (%)	More than 1/3 being treated for hypertension 71 (0.6) 100%		Overall mortality stratified by 25(OH)D tertiles	X	X	X	X	X	X
Pilz 2009[73] Hoorn Study Netherlands	• Health status • Mean Age (range), y • Male (%)	More than 20% Type 2 Diabetes or impaired glucose tolerance 69.2 (6.5) 50%		All-cause mortality stratified by 25(OH)D quartiles		X	X	X	X	X
Semba 2010[93] InCHIANTI Italy	• Health status • Mean Age (range), y • Male (%)	Nd 78 (72–85) 67.3%		All-cause mortality and cardiovascular mortality stratified by 25(OH)D quartiles		X	X		X	X
Signorello 2013[74] Southern Community Cohort Study US	• Health status • Mean Age (range), y • Male (%)	nd nd nd		All-cause mortality stratified by 25(OH)D quartiles			X			X

Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Smit 2012[213] NHANES III US (various)	• Health status • Mean Age (SD), y • Male (%)	Malnourished/frailty, pre-frail, not frail 69.4 (SD 0.3) 46.5%		All-cause mortality stratified by 25(OH)D quartiles		X	X	X	X	X
Szulc 2009[214] MINOS Study Montceau les Mines, France	• Health status • Mean Age (SD), y • Male (%)	nd 64 (SD 7) 55%		Mortality stratified by 25(OH)D quartiles	X	X	X	X		X
Szulc 2009[215] MINOS Study Montceau les Mines, France	• Health status • Mean Age (SD), y • Male (%)	nd 64 (SD 7) 100%		Mortality stratified by 25(OH)D quartiles		X	X	X		X
Virtanen 2011[216] Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study Finland	• Health status • Mean Age (range), y • Male (%)	Post-menopausal, 54–62% hypertension 61.8 (53.4–72.7/SD 6.2) 48.6%		Overall mortality stratified by 25(OH)D tertiles		X	X	X		X
Welsh 2012[60] MIDSPAN Family Study Renfrew and Paisley, UK	• Health status • Mean Age (range), y • Male (%)	vitamin D not deficient 45.2 (6.2) 46%		All-cause mortality stratified by 25(OH)D tertiles	X	X	X	X	X	X
Tomson 2013[75] Whitehall study London, UK	• Health status • Mean age (SD), y • Male (%)	self-reported health good/excellent 77.4% 76.9 (SD 4.9) 100%		Death (all non-vascular) and Death (al causes) stratified by 25(OH)D doubling concentration			X	X		X
Skaaby 2013[86] Monica10 and Inter99 Denmark	• Health status • Mean age (SD), y • Male (%)	NR Monica 10: 55.4 Inter 99: 46.1 Monica 10: 50.2 Inter 99: 49.2		All-cause mortality stratified by 25(OH)D quartiles		X		X	X	X

Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Wong 2013[217] Australia	• Health status • Mean age (SD), y • Male (%)	NR 76 (70–88) 100%		All-cause mortality stratified by 25(OH)D quartiles		X	X	X		X
Sempos 2013[218] NHANES III US	• Health status • Mean age (SE), y • Male (%)	NR 45 (SE 0.47) 49%		All-cause mortality stratified by 25(OH)D in 9 categories		X			X	
Schottker 2013[76] ESTHER Germany	• Health status • Mean age (SD), y • Male (%)	NR 62 (SD 6.5) 43.8%		All-cause mortality stratified by 25(OH)D tertiles	X	X		X	X	X
Formiga 2014[77] Octabaix Spain	• Health status • Mean age (SD), y • Male (%)	Oldest old 85 (SD 0) 39.4%		Total mortality stratified by 25(OH)D quartiles		X		X		

[A]Fracture Risk Epidemiology in the Elderly
[B]~40% with CVD and ~60% arthritis

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for trend	Study Quality
Jia 2007[219] UK (57°N) [17442130]	>75, both sexes	Mortality	69	25(OH)D	6.0–23.0 (M)/ 7.0–19.0 (F)	41	75	1.74	0.91, 3.34	0.03	B
					23.1–30.0 (M)/ 29.1–24.0 (F)	34	86	1.4	0.73, 2.70		
					30.1–37.0 (M)/ 24.1–30.2 (F)	21	80	0.9	0.45, 1.79		
					37.1–47.0 (M)/ 30.3–39.0 (F)	17	78	0.8	0.39, 1.62		
					47.1–82.0 (M)/ 39.1–82.0 (F)	16	79	**1**	**Reference**		
Sambrook 2004 & 2006[220,221] FREE[A] Australia (33°S) [15531500 & 16598375]	>65, both sexes	Mortality	27	25(OH)D	NA	559	1112	0.87[B]	0.75, 1.01	nd	C
Visser 2006[222] Longitudinal Aging Study Netherlands (52°N) [16960177]	>65, both sexes	Mortality	72	25(OH)D	<25	66	127	1.28	0.85, 1.92	0.19	C
					25–49.9	42	462	1	0.72, 1.40		
					50–74.9	30	440	0.91	0.65, 1.26		
					≥75	29	231	**1**	**Reference**		
Melamed 2008[85] NHANES III US (various) [18695076]	>20, both sexes	Mortality	104	25(OH)D	<17.8	nd	nd	1.26	1.08, 1.46	nd	C
					17.8–24.3	nd	nd	1.06	0.89, 1.24		
					24.4–32.1	nd	nd	0.93	0.79, 1.10		
					>32.1	nd	nd	**1**	**Reference**		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for trend	Study Quality
Melamed 2008[85] NHANES III US (various) [18695076]	>20, men only	Mortality	104	25(OH)D	<17.8	nd	nd	1.04	0.83, 1.30	nd	C
					17.8–24.3	nd	nd	0.94	0.75, 1.19		
					24.4–32.1	nd	nd	0.82	0.64, 1.05		
					>32.1	nd	nd	**1**	**Reference**		
Melamed 2008[85] NHANES III US (various) [18695076]	>20, women only	Mortality	104	25(OH)D	<17.8	nd	nd	1.55	1.15, 1.98	nd	C
					17.8–24.3	nd	nd	1.27	0.97, 1.66		
					24.4–32.1	nd	nd	1.16	0.87, 1.55		
					>32.1	nd	nd	**1**	**Reference**		
Melamed 2008[85] NHANES III US (various) [18695076]	20–65, both sexes	Mortality	104	25(OH)D	<17.8	nd	nd	1.28	0.93, 1.76	nd	C
					17.8–24.3	nd	nd	1.13	0.81, 1.56		
					24.4–32.1	nd	nd	0.81	0.58, 1.14		
					>32.1	nd	nd	**1**	**Reference**		
Melamed 2008[85] NHANES III US (various) [18695076]	³65, both sexes	Mortality	104	25(OH)D	<17.8	nd	nd	1.26	1.03, 1.54	nd	C
					17.8–24.3	nd	nd	0.99	0.82, 1.20		
					24.4–32.1	nd	nd	0.97	0.79, 0.82		
					>32.1	nd	nd	**1**	**Reference**		
NEW studies											
Bolland 2010[58] New Zealand	Post-menopausal women	Primary-Death	5 yrs	25(OH)D	<50 nmol/L	13	373	HR=0.90	0.4, 2.0	0.82	A
					≥50 nmol/L	16	366	1.00	**Reference**		
Cawthon 2010[98] MrOS (multisite) US	Men (51-70 yrs; ≥71 years)	all-cause mortality	7.3 yrs	25(OH)D	Quartile 1: <49.75 nmol/L		372	HR=0.95	0.68, 1.34	0.961	B
					Quartile 2: ≥49.75 to <63.0 nmol/L		370	1.05	0.75, 1.47		
					Quartile 3: ≥63.0 to <75.0 nmol/L		372	0.89	0.64, 1.24		
					Quartile 4: ≥75.0		376	1.00	**Reference**		
					Deficient, <50 nmol/L		376	0.94	0.67, 1.32	0.706	
					Insufficient, 50 to <75 nmol/L		737	0.97	0.72, 1.30		
					Sufficient, ≥75 nmol/L		377	1.00	**Reference**		
					per SD decrease			1.01	0.89, 1.14		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for trend	Study Quality
de Boer 2012[87] Cardiovascular Health Study US (various)	White older adults	Death	11 yrs	25(OH)D	Normal level	539	1126	HR=1.00	**Reference**	NR	A
					Low level (season specific, ranges 43–61 nmol/L)	287	495	1.32	1.14, 1.53		
Eaton 2011[70] WHI substudy US (multisite)	Post-menopausal women 50–79 years	all-cause mortality	10 yrs	25(OH)D	Quartile 1: 3.25–36.50 nmol/L		608	HR=1.25	0.80–1.95	0.39	A
					Quartile 2: 36.51–49.95 nmol/L		606	1.13	0.73–1.75		
					Quartile 3: 49.96–65.38 nmol/L		608	1.17	0.75–1.81		
					Quartile 4: 65.39–146.67 nmol/L		607	1.00	**Reference**		
Fedirko 2012[101] EPIC US (4 sites)	Men and women (diagnosed at an average age of 62)	overall mortality	73 mos	25(OH)D	<36.3	128	242	HR=1.00	**Reference**	<0.01	B
					36.4–48.6	108	239	0.82	0.63, 1.07		
					48.7–60.5	117	241	0.91	0.70, 1.18		
					60.6–76.8	95	240	0.78	0.59, 1.03		
					>76.8	93	240	0.67	0.50, 0.88		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for trend	Study Quality
Hutchinson 2010[79] Tromsø Study (Norway)	Men(55–74 yrs) Women (50–74 yrs)	all-cause death	11.7 yrs	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)	247	1184	HR=1.32	1.07–1.62	NR	
nonsmokers					Quartile 2: mean=46.7 (sd=6.0)	198	1187	1.06	0.86–1.31		
					Quartile 3: mean=56.2 (sd=6.0)	190	1192	1.09	0.88–1.34		
					Quartile 4: mean=72.3 (sd=13.2)	163	1188	1.00	**Reference**		B
smokers		all-cause death	11.7 yrs	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)	156	597	1.06	0.83–1.35	NR	
					Quartile 2: mean=46.7 (sd=6.0)	143	606	0.97	0.76–1.25		
					Quartile 3: mean=56.2 (sd=6.0)	138	607	1.04	0.81–1.33		
					Quartile 4: mean=72.3 (sd=13.2)	124	600	1.00	**Reference**		
Jacobs 2011[144] Women's Healthy Eating and Living Well (WHEL) Study	Breast cancer survivors who had completed primary treatment of early stage breast cancer within the previous 4 years	mortality	7.3 yrs	25(OH)D	Insufficient, <50 nmol/L	164		1.13	0.72, 1.79	0.59	B
					Sufficient, ≥50 nmol/L	336		1.00	**Reference**		
Johansson 2012[211] MrOS (Sweden)	Men (70–81 yrs)	death	8.2 yrs	25(OH)D	per SD decrease	577	2878	HR=1.16	1.06, 1.26	NR	A
Kestenbaum 2011[81] Cardiovascular Health Study	>65 years	Primary-all-cause mortality	14 yrs	25(OH)D	>75 nmol/L	329	681	HR=1.00	**Reference**		B
					37.5–75.0 nmol/L	668	1247	1.15	1.00, 1.33		
					<37.5 nmol/L	229	384	1.29	1.05, 1.57		
					continuous per 25 nmol/L	1226	2312	1.09	1.02, 1.17	0.012	

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for trend	Study Quality
Kritchevsky 2012[212] Health, Aging, and Body Composition (ABC) Study	Older community dwelling men and women (70–79 yrs)	all-cause mortality	8.5 yrs	25(OH)D	< 25 nmol/L	44	108	HR=2.27	1.59, 3.24	<0.001	B
					25 to <50 nmol/L	241	750	1.48	1.20, 1.84		
					50 to <75 nmol/L	229	931	1.25	1.02, 1.52		
					≥75 nmol/L	177	849	1.00	**Reference**		
whites		all-cause mortality	8.5 yrs	25(OH)D	< 25 nmol/L	10	25	2.02	1.02, 3.99	0.001	
					25 to <50 nmol/L	82	279	1.54	1.16, 2.06		
					50 to <75 nmol/L	138	620	1.22	0.96, 1.55		
					≥75 nmol/L	143	691	1.00	**Reference**		
blacks		all-cause mortality	8.5 yrs	25(OH)D	<25 nmol/L	34	83	2.59	1.57, 4.26	<0.001	
					25 to <50 nmol/L	159	471	1.76	1.20, 2.57		
					50 to <75 nmol/L	91	311	1.60	1.07, 2.39		
					≥75 nmol/L	34	158	1.00	**Reference**		
Lin 2012[83] General Population Trial of Linxian (China)	Men 40–69 yrs	all-cause mortality	24 yrs	25(OH)D	continuous 25(OH)D	793	1101	HR=1.01	0.97, 1.05	0.735	B
						479	608	0.99	0.94, 1.04	0.7	
	Women 40–69 yrs					314	493	1.03	0.97, 1.10	0.348	
Michaelsson 2010[84] Uppsala Longitudinal Study of Adult Men Uppsala (Sweden)	Elderly men birth 1920–1924	overall mortality	12.7 yrs	25(OH)D	< 10th percentile (<46 nmol/L)	76	119	HR=1.43	1.11, 1.84		B
					10th–90th percentile (46–93 nmol/L)	444	956	1.00	**Reference**		
					>90th percentile (>93 nmol/L)	64	119	1.27	0.97, 1.66		
Pilz 2009[73] Hoorn Study Netherlands	Men and women (50–75 yrs)	all-cause mortality	6.2 yrs	25(OH)D	1st quartile (mean 25(OH)D 30.6 nmol/L)	21	152	HR=1.97	1.08, 3.58	0.027	B
					2nd–4th quartiles (mean 25(OH)D 45.6–78.9)	30	462	1.00	**Reference**		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for trend	Study Quality
Semba 2010 [93] InCHIANTI Italy		all-cause mortality	6.5 yrs	25(OH)D	1st quartile: <26.3 nmol/L	NR	252	HR 2.11	1.22, 3.64		
					2nd quartile: 26.3–40.0 nmol/L	NR	254	HR 1.41	0.83, 2.40		
					3rd quartile: 40.3–64 nmol/L	NR	247	HR 1.12	1.09, 1.15		
					4th quartile: >64 nmol/L	NR	253	HR 1.00	**Reference**		
Signorello 2013[74] Southern Community Cohort Study US	Men and women (40–79 yrs)	all-cause mortality	1 yr or more	25(OH)D	Quartile 4: (>54.1nmol/L)	364	827	1.00	**Reference**	<0.001	A
					Quartile 3: (37.9–54.1 nmol/L)	405	868	1.17	0.95, 1.45		
					Quartile 2: (25.5–37.9 nmol/L)	482	945	1.41	1.14, 1.74		
					Quartile 1: <25.5 nmol/L)	601	1064	1.80	1.43, 2.27		
African Americans		all-cause mortality	1 yr or more	25(OH)D	Quartile 4: (>54.1nmol/L)	181	400	1.00	**Reference**	0.003	
					Quartile 3: (37.9–54.1 nmol/L)	266	565	1.15	0.87, 1.53		
					Quartile 2: (25.5–37.9nmol/L)	353	730	1.19	0.91, 1.57		
					Quartile 1: <25.5 nmol/L)	475	855	1.60	1.20, 2.14		
non-African Americans		all-cause mortality	1 yr or more	25(OH)D	Quartile 4: (>54.1nmol/L)	179	419	1.00	**Reference**	<0.001	
					Quartile 3: (37.9–54.1 nmol/L)	136	296	1.09	0.78, 1.52		
					Quartile 2: (25.5–37.9 nmol/ L)	129	214	1.99	1.37, 2.90		
					Quartile 1: <25.5 nmol/L)	122	203	2.11	1.39, 3.21		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for trend	Study Quality
Smit 2012[213] NHANES III	Adults (60 and over)				Quartile 1: <49.5 nmol/l	NR	NR	2.98	2.01, 4.42		
frail		mortality	12 yrs	25(OH)D	Quartile 2: 49.5–66.4 nmol/l	NR	NR	2.37	1.44, 3.89		
					Quartile 3: 66.5–84.1 nmol/l	NR	NR	2.50	1.48, 4.21		
					Quartile 4: >84.1 nmol/l	NR	NR	1.43	0.83, 2.46		
pre-frail		mortality	12 yrs	25(OH)D	Quartile 1: <49.5 nmol/l	NR	NR	1.97	1.61, 2.40		A
					Quartile 2: 49.5–66.4 nmol/l	NR	NR	1.62	1.29, 2.03		
					Quartile 3: 66.5–84.1 nmol/l	NR	NR	1.51	1.16, 1.97		
					Quartile 4: >84.1 nmol/l	NR	NR	1.82	1.41, 2.35		
not frail		mortality	12 yrs	25(OH)D	Quartile 1: <49.5 nmol/l	NR	NR	1.25	0.97, 1.60		
					Quartile 2: 49.5–66.4 nmol/l	NR	NR	1.20	0.96, 1.49		
					Quartile 3: 66.5–84.1 nmol/l	NR	NR	1.11	0.88, 1.40		
					Quartile 4: >84.1 nmol/l	NR	NR	1.00	**Reference**		
Szulc 2009[214] MINOS Study	Men(50 yrs and over)	mortality	10 yrs	25(OH)D	per SD decrease	600	782	1.22	1.01, 1.48		A
					Quartile 1 <65 nmol/l summer or <40 nmol/l other months	NR	NR	1.44	1.03, 2.03		
					Quartiles 2–4	NR	NR	1.00	**Reference**		
Szulc 2009[215] MINOS Study	Men(50 yrs and over)	mortality	10 yrs	25(OH)D	Quartile 1	NR	NR	1.6–1.8	NR	<0.05	A
					Quartiles 2–4	NR	NR	1.00	**Reference**		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for trend	Study Quality
Virtanen 2011[216] Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study Finland	Men (average age 61.8)	mortality	9.1 yrs	25(OH)D	Tertile 1: 8.9–34.0 nmol/L	39	379	2.06	1.12, 3.80	0.02	A
					Tertile 2: 34.1–50.8 nmol/L	31	378	1.68	0.92, 3.07		
					Tertile 3: 50.9–112.8 nmol/L	17	379	1.00	**Reference**		
Welsh 2012[60] MIDSPAN Family Study Scotland	Men and women	Primary-all-cause mortality	14.4 yrs	25(OH)D	per 1 SD increase	70	1492	0.74	0.56, 0.99		B
					Deficient, <37.5 nmol/L	NR	689	2.02	1.17, 3.51		
					Not deficient ≥37.5 nmol/L	NR	803	1.00	**Reference**		
Tomson 2013[75] Whitehall study		Death, all non-vascular	13.1 yrs	25(OH)D	Doubling Concentration	1857	5409	0.77	0.69, 0.86		B
		Death, all causes				3215	5409	0.78	0.72, 0.85		
Skaaby 2013[86] Monica10 and Inter99		all-cause mortality	10 yrs	25(OH)D	per 10nmol/L	633	8329	0.95	0.92, 0.99	0.005	B
					Q1			1.00	**Reference**	0.041	
					Q2			0.79	0.64, 0.98		
					Q3			0.81	0.65, 1.01		
					Q4			0.73	0.57, 0.92		
Wong 2013[217]		all-cause mortality	6.7 yrs	25(OH)D	per 10nmol/L decrease in 25(OH)D	1144	4203	1.04	1.01, 1.07		B
					halving of 25(OH)D			1.21	1.08, 1.35		
					Q1: 10–52.8			1.20	1.02, 1.42		
					Q2: 52.9–67.3			1.00	**Reference**		
					Q3: 67.4–81.6			0.99	0.84, 1.17		
					Q4: 81.7–238.4			0.99	0.83, 1.17		

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for trend	Study Quality
Sempos 2013[218]					<20	79	251	1.6	1.2, 2.2		
NHANES III					20–29	297	1270	1.5	1.2, 1.8		
					30–39	592	2340	1.3	1.1, 1.5		
		death			40–49	694	2790	1.1	0.96, 1.3		
		from all-	15 yrs	25(OH)D	50–59	668	2526	1.2	1.01, 1.30		A
		cause			60–74	775	3046	1.1	0.99, 1.30		
					75–99	533	2156	1.0	**Reference**		
					100–119	110	518	1.1	0.9, 1.4		
					>=120	36	202	1.4	0.9, 2.2		
Schottker 2013[76]					<30	238	1444	1.68	1.41, 2.01		
ESTHER					30–50	448	4199	1.17	1.01, 1.35		
					>50	397	3935	1.00	**Reference**		
					<30	142	609	1.41	1.13, 1.77		
	>=65 yrs of age	all-cause mortality	9.5 yrs	25(OH)D	30–50	269	1706	1.09	0.90,1.31		B
					>50	236	1394	1.00	**Reference**		
					<30	238	835	2.08	1.58, 2.76		
	<65 yrs of age				30–50	448	2493	1.30	1.04, 1.63		
					>50	397	2541	1.00	**Reference**		
Formiga 2014[77]					Q1: <34.94	15	71	1.28	0.61, 2.6	0.41	
Octabaix		total	2.8 yrs	25(OH)D	Q2: 34.94–61.65	18	77	1.36	0.67, 2.74		B
		mortality			Q3: 61.66–83.37	11	84	0.76	0.34, 1.68		
					Q4:>83.37	14	80	1.00	**Reference**		

[A]Fracture Risk Epidemiology in the Elderly
[B]Per unit change in the log-transformed concentration.

Vitamin D and Hypertension and Blood Pressure

We searched for systematic reviews and primary studies that evaluated associations between vitamin D supplementation or serum concentrations and incidence of hypertension and change in blood pressure. For the outcome *incidence of hypertension*, we reviewed RCTs and other longitudinal studies. For the outcome *change in blood pressure*, we reviewed only RCTs. The EPC and the TEP agreed that due to the large volume of literature, the limited resources would not be expended on reviewing observational studies for the surrogate outcome blood pressure. We included only studies of adults. Studies of pregnancy-related hypertension and blood pressure control are included in the "Pregnancy-related outcomes" section.

Hypertension

Synopsis

No systematic reviews evaluated the association between vitamin D intake or serum 25(OH)D concentrations and incidence of hypertension. **A large prospective cohort study identified for the current report that evaluated the association between serum 25(OH)D concentration and the risk for hypertension using the Intermountain database found a highly significant association of very low and low baseline serum 25(OH)D concentrations and the prevalence of hypertension at an average of 1.3 years followup. An assessment of the association between serum 25(OH)D and incident hypertension in 1,211 participants in the Physicians' Health Study at a mean followup of 15.3 years (maximum 27 years) showed a marginally significant j-shaped association.** A combined analysis of a small subset of the Health Professionals Followup (HPFS) and Nurses Health Studies (NHS) evaluated the association with serum 25(OH)D concentrations. The analysis found higher incidence of hypertension at 4 and 8 years in men with baseline 25(OH)D concentration less than 37.5 nmol/L (OR~3–6). In women, serum 25(OH)D concentrations less than 37.5 nmol/L also had a significantly higher incidence of hypertension at 4 years (OR~3), but not at 8 years (OR~1.5).

Detailed Presentation (Tables 40 & 41)

A prospective cohort study identified for the current report analyzed records of 19,128 patients, age 50 and over, in the Intermountain Database for which baseline serum 25(OH)D concentrations were available (25% male) (rated C). Those with serum 25(OH)D concentrations less than 37.5 nmol/L and between 40 and 75 nmol/L were significantly more likely than those with normal serum 25(OH)D concentrations (>75 nmol/L) (HR 1.62, HR 1.18, respectively) to have hypertension within an average followup time of 1.3 years. No subgroup analyses were done by sex or age.[223] An assessment of the association between serum 25(OH)D and incident hypertension in 1,211 participants in the Physicians' Health Study (men of mean age 57.6) at a mean followup of 15.3 years (maximum 27 years) showed a marginally significant j-shaped association, with men in the lowest two quartiles and in the highest quartile at higher risk for incident hypertension than those in the third quartile (rated A).[224]

One analysis (methodological quality B) **identified for the original report** evaluated the incidence of hypertension in a combined set of 613 men from the HPFS and 1198 women from the NHS who had serum 25(OH)D concentrations measured.[225] The men were on average 65 years old and the women 57 years old. Among the men at 4 years, those with serum 25(OH)D

concentrations less than 37.5 nmol/L were significantly more likely to have new onset hypertension than either men with 25(OH)D concentrations above 75 nmol/L (OR=6.1) or above 37.5 nmol/L (OR=5.7). The association remained significant at 8 years, although with a smaller effect size (OR=3.5 and 3.0, respectively). In women, a similar, though weaker, effect was seen at 4 years, such that those with 25(OH)D concentrations less than 37.5 nmol/L were significantly more likely to have new onset hypertension than either women with 25(OH)D concentrations above 75 nmol/L (OR=2.7) or above 37.5 nmol/L (OR=3.0). However, this effect was smaller and nonsignificant at 8 years (OR=1.7 and 1.4, respectively). The study was limited primarily by its inclusion of only a relatively small subset of participants and its reliance on self-reported hypertension without assessment of blood pressure measurements.

In the second analysis by the same investigators, the NHS 2 study was analyzed for the association between serum 25(OH)D concentration and hypertension as a nested case-control study.[226] These women were on average 43 years old. Cases and controls (per the 2005 biennial questionnaire) were chosen from among those women without hypertension, cardiovascular disease, diabetes, obesity, or cancer at baseline (blood samples drawn from 1997 to 1999). After approximately 7 years, a statistically significant trend was found such that women in the three quartiles with serum 25(OH)D concentrations of 80.5 nmol/L or less were about 50 to 60 percent more likely to develop hypertension than those women with higher serum concentrations of 25(OH)D (adjusted OR = 1.52 to 1.66, each of which was statistically significant compared to the highest quartile). The study was graded methodological quality B for similar reasons as the analysis of the HPFS and NHS studies.

Findings per Vitamin D Concentration

The Intermountain data were analyzed with 25(OH)D cutpoints of 37.5 and 75 nmol/L. Significant associations were identified for those with serum concentrations below 75 nmol/L. The HPFS and NHS studies were analyzed with 25(OH)D cutpoints of 37.5 and 75 nmol/L. Significant associations were found for those with serum concentrations below 37.5 nmol/L. The NHS 2 study was analyzed with 25(OH)D quartiles, such that significant associations were found for those with serum concentrations of 80.5 nmol/L or less.

Findings per Age and Sex

See above *Detailed presentation* of the HPFS and NHS for the separate analyses by sex. No subgroup analyses were reported by life stage. The participants in the studies were approximately 40 to 80 years old.

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  Not reviewed **19–50 y** The NHS 2 included all women within the life stage. After approximately 7 years, those with serum 25(OH)D concentrations of 80.5 nmol/L or less were about 50 to 60 percent more likely to develop hypertension.

- **51–70 y**
  Individuals 50 and over with serum 25(OH)D concentrations less than 75nmol/L, identified in the Intermountain Health Database for the current study, had higher prevalence of hypertension at 1.3 years (average) followup. No subgroup analysis was conducted to further assess individuals over 70 or risk by sex. An assessment of the association between serum 25(OH)D and incident hypertension in men in the Physicians' Health Study (mean age 57.6) at a mean followup of 15.3 years (maximum 27 years) showed a marginally significant j-shaped association, with men in the lowest two quartiles and in the highest quartile at higher risk for incident hypertension than those in the third quartile. HPFS and NHS included participants mostly within this life stage. In men and women, the study found higher incidence of hypertension at 4 years follow up in those with serum 25(OH)D concentrations less than 37.5 nmol/L; at 8 years, the association was significant only for men.
- **≥71 y**
  A minority of the men and few of the women appear to have been in this life stage. No unique conclusions are possible for this life stage separate from those for people 51 to 70 years.
- **Postmenopause**
  The majority of the women in NHS were postmenopausal. A significant association between serum 25(OH)D concentrations less than 37.5 nmol/L and increased hypertension was found at 4 years, but not 8 years follow up.
- **Pregnant & lactating women**
  Not reviewed

Table 40. Vitamin D and hypertension: Characteristics of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Forman 2007[225] HPFS, NHS US (various) [17372031]	• Health status • Mean age (SD), y • Male (%)	Any Men 65 (8) Women 57 (7) 34	• Assay method • Season blood drawn	RIA All	Hypertension incidence stratified by 25(OH)D categories (2 and 3 categories)		X	X			X	
Forman 2008[226] NHS 2 US (various) [18838623]	• Health status • Mean age (SD), y • Male (%)	No HTN, CVD, DM, obesity, cancer 43 (40–46) 0	• Assay method • Season blood drawn	EIA All	Hypertension incidence stratified by 25(OH)D categories (2 and 3 categories)	X	X	X		X		
NEW Cohort Study												
Anderson 2010[223] US	• Health status • Mean age (SD), y • Male (%)	nd 55 (21) 25.2%	• Assay method • Season blood drawn	EIA All	Hypertension incidence stratified by 25(OH)D categories (2 and 3 categories)							
Wang 2013[224] Physicians' Health Study (PHS) US	• Health status • Mean age (SD), y • Male (%)	Healthy 57.6 (SD 7.6) 100%	• Assay method • Season blood drawn	EIA All	Hypertension incidence stratified by 25(OH)D quartiles	X	X	X			X	

Table 41. Vitamin D and hypertension: Results of cohort and nested case-control studies (updated from original report)

Author Year Study Name [PMID]	Mean (SD) Age, Sex	Outcome (n/N; Incidence)	Followup Duration	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR, HR, RR	95% CI	P for Trend	Study Quality
Men											
Forman 2007[225] HPFS [17372031]	65 (8), Men	Hypertension (61/613; 0.100)	4 y	25(OH)D	<37.5	6	33	6.13	1.00, 37.8*	nd	B
					37.5–75	33	247	1.12	0.51, 2.48		
					≥75	22	233	**1**	**Reference**		
					<37.5	6	33	5.68	1.01, 32.3*	<0.05	
					≥37.5	55	580	**1**	**Reference**		
		Hypertension (131/613; 0.214)	8 y	25(OH)D	<37.5	9	33	3.53	1.02, 12.3*	nd	
					37.5–75	nd	247	nd	nd		
					≥75	nd	233	**1**	**Reference**		
					<37.5	9	33	3.03	0.94, 9.76	NS	
					≥37.5	124	580	**1**	**Reference**		
Women											
Forman 2008[226] NHS 2 [18838623]	43 (40–46, range), Women	Hypertension (742 cases; 742 controls) Nested case control	~7 y	25(OH)D	41.75 (15.5–52.5)	208	371	1.66	1.11, 2.48	0.01	B
					59.5 (52.75-66.25)	188	370	1.55	1.07, 2.23		
					73.0 (66.5–80.5)	195	374	1.52	1.06, 2.18		
					94.75 (80.75–224)	151	369	**1**	**Reference**		

Table 41. Vitamin D and hypertension: Results of cohort and nested case-control studies (updated from original report) (continued)

Author Year Study Name [PMID]	Mean (SD) Age, Sex	Outcome	Followup Duration	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR, HR, RR	95% CI	P for Trend	Study Quality
Forman 2007[225] NHS [17372031]	57 (7), Women	Hypertension (129/1198; 0.108)	4 y	25(OH)D	<37.5	11	nd[A]	2.67	1.05, 6.79*	nd	B
					37.5–75	60	nd	0.85	0.53, 1.34		
					≥75	58	nd	**1**	**Reference**		
					<37.5	11	nd	2.98	1.24, 7.20*	<0.05	
					≥37.5	118	nd	**1**	**Reference**		
		Hypertension (274/613; 0.229)	8 y	25(OH)D	<37.5	20	nd[A]	1.7	0.92, 3.16	nd	
					37.5–75	nd	nd	nd	nd		
					≥75	nd	nd	**1**	**Reference**		
					<37.5	20	nd	1.42	0.79, 2.56	NS	
					≥37.5	254	nd	**1**	**Reference**		
NEW Cohort Studies											
Anderson 2010[223] US	19–50, 51–70 yrs	Hypertension	1.3 yrs on average	serum 25(OH)D	very low (Vit D level ≤37.5 nmol/L)	7848	15,121	HR= 1.62	1.38, 1.89	p<0.0001	B
					low (Vit D level 56–75 nmol/L	8530	19,474	1.18	1.05, 1.33	p=0.005	
					normal (Vit D level > 75 nmol/L)	2750	6,909	**1**			
Wang 2013[224] Physicians' Health Study (PHS)		Hypertension	15.3 yrs	25(OH)D	Q1: 13.0–57.8	97	164	**1.00**	**Reference**	0.43	A
					Q2: 37.0–74.9	97	164	0.94	0.69, 1.27		
					Q3: 48.6–93.5	79	167	0.69	0.50, 0.96		
					Q4: 68.8–167.2	94	165	0.82	0.60, 1.13		
					<50	73	136	**1.00**	**Reference**	0.32	
					50–74	144	244	1.03	0.75, 1.42		
					75–99	93	178	0.79	0.56, 1.11		
					>=100	57	102	0.94	0.62, 1.40		
				1,25(OH)D	Q1: 29.9–79.3	87	162	**1.00**	**Reference**	0.16	
					Q2: 68.0–88.2	80	162	0.92	0.66, 1.27		
					Q3: 80.8–101.8	95	165	1.12	0.82, 1.54		
					Q4: 94.0–177.6	101	162	1.19	0.86, 1.63		

* Statistically significant (P<0.05).

[A] Due to formatting error in study table, no data on numbers of women in each category.

Vitamin D and Blood Pressure

Synopsis

No qualified systematic reviews have evaluated the association between vitamin D intake or serum 25(OH)D concentrations and changes in blood pressure. **The current study identified ten RCTs that assessed the effects of one or more dosage levels of vitamin D compared with placebo on blood pressure in adults. Dosages ranged from 125IU to 7000IU per day. Followup ranged from 3 months to one year. Participants included postmenopausal women, middle aged U.S. blacks, overweight young Chinese and Danish adults, healthy South Asian women residing in the UK, and healthy young women. Of the ten RCTs, no effect of vitamin D supplementation was observed in seven, vitamin D significantly decreased systolic blood pressure in two studies (both systolic and diastolic in one of those two), and in the tenth, systolic blood pressure actually increased slightly in the supplemented group.**

Three trials from Germany, UK, and India **identified for the original report** compared different doses of vitamin D (800 IU daily, a single dose of 100,000 IU, or 120,000 IU every 2 weeks) with placebo, with or without supplemental calcium in both groups. The study participants also varied: either older men, older men and women, or men mostly in their 40s. Both recruited older adults (over 63 or 70 years). All trials reported no significant effect on diastolic blood pressure. The A quality British study of a single dose of vitamin D 100,000 IU found no difference in systolic blood pressure after 5 weeks. The B quality German study found a significant net reduction of 7 mm Hg after 8 weeks in older women taking vitamin D 800 IU daily. The B quality Indian study of obese men mostly in their 40s, found a nearly significant net increase of 4 mm Hg after 6 weeks of vitamin D 120,000 IU every 2 weeks. No long term data were available.

Detailed Presentation (Tables 42 & 43)

Of the ten RCTs identified for the current report, one RCT found a decrease in systolic blood pressure of 0.2mm Hg for every 25nmol/L increase in supplemental plasma vitamin D. This U.S. trial randomized 283 overweight and obese (but otherwise healthy) black adults, 44 to 59 years of age and 63% female, to 1000, 2000, or 3000 IU/day cholecalciferol or placebo for 3 months (study rated A). Supplementation did not affect diastolic blood pressure. The effect was greater for those with lower baseline 25(OH)D concentrations but did not differ by baseline blood pressure. No subgroup analysis was performed by sex or use of antihypertensives.[227] One Spanish 16-week RCT that supplemented healthy young women (18 to 35 years of age) with 200 IU vitamin D per day found a decrease in both systolic blood pressure (compared with 8-week levels) and diastolic blood pressure (compared with baseline) (rated B).[228] Eight RCTs reported no effect on or an increase in systolic blood pressure (three rated A, two rated B, and one rated C).[229-236]

In the original report, the A quality trial of single-dose vitamin D, performed in Cambridge, UK, recruited older adults (63 to 76 years, mean 70 years) who were not taking antihypertensive medications.[237] During the winter, they were given either a one-time dose of vitamin D_3 (100,000 IU [2.5 mg]) or placebo, and blood pressure was rechecked at 5 weeks. In both study arms, systolic and diastolic blood pressures fell by equal amounts, resulting in no net difference between vitamin D supplemented and placebo groups. No subgroup analyses were reported.

The German B quality trial of supplementation with combined vitamin D and calcium versus calcium alone recruited older women (70 to 86 years) without severe hypertension.[238] For 8 weeks, the women took either vitamin D_3 800 IU and calcium carbonate 1200 mg or calcium carbonate 1200 mg alone daily. Systolic blood pressure decreased by 13 mm Hg in those supplemented with vitamin D and calcium compared with a 6 mm Hg decrease in those taking calcium alone (P=0.02). Diastolic blood pressure declined by 7 mm Hg in both groups. No subgroup analyses were reported. The study was limited by inadequate reporting of its study methods and lack of blinding.

The Indian B quality study compared every other week vitamin D_3 supplementation 120,000 IU with placebo for 3 weeks in generally healthy but obese men without hypertension.[96] The men who received the vitamin D supplements had a net increase in systolic blood pressure of 4 mm Hg, which was close to statistically significant (P=0.06), but no significant difference in diastolic blood pressure. The study was limited by a high dropout rate (26 percent).

Findings per Intake Level

No conclusions can be reached about an intake level threshold. In individual trials, a single dose of 100,000 IU of cholecalciferol had no significant effect on systolic and diastolic blood pressure after 5 weeks, a daily dose of vitamin D_3 800 IU together with calcium significantly lowered systolic blood pressure more than calcium alone, but every other week vitamin D_3 120,000 IU resulted in a nearly statistically significant increase in systolic blood pressure.

Findings per Age and Sex

No conclusions can be reached about differences in effect based on age or sex. **None of the studies identified for the current report stratified by age or sex.** The study of older women **identified for the original report** found a significant decrease in systolic blood pressure with relatively low dose vitamin D, a higher dose study of similarly aged men and women found no effect on blood pressure, and the highest dose study of men mostly in their 40s found an increase in systolic blood pressure.

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  Not reviewed
- **19–50 y**
  One study of black U.S. residents 44–59 years of age found significant decreases in systolic blood pressure with vitamin D supplementation. A study of Spanish women 18–50 years found significant decreases in both systolic and diastolic blood pressure with modest daily supplementation. Eight studies identified for the current report, including those of overweight Chinese young adults, ages 18 to 25 years, and overweight Norwegian adults, 21 to 70 years of age found no effect of vitamin D supplementation on blood pressure. A single study of men in this life stage found a

near significant increase in systolic blood pressure with vitamin D and no effect on diastolic blood pressure.

- **51–70 y**
  One trial included people with an average age of 70 years, implying that about half were within this life stage. No significant effect on blood pressure was found of a single large dose of vitamin D.
- **≥71 y**
  Both trials included people within this life stage. The trial of people with an average age of 70 years found no significant effect of a single large dose of vitamin D. The single trial of women over age 70 years found a significant benefit for systolic blood pressure for vitamin D_3 800 IU and calcium carbonate 1200 mg compared with calcium carbonate 1200 mg alone.
- **Postmenopause**
  A study identified for the current report of healthy postmenopausal women (60–70 years of age) reported no effect of vitamin D supplementation on blood pressure, although serum 25(OH)D concentrations varied significantly with season of blood draw. The women in both trials were postmenopausal. See the ≥71 y life stage.
- **Pregnant & lactating women**
  Not reviewed

Table 42. Vitamin D and blood pressure: Characteristics of RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Scragg 1995[237] Cambridge, UK (52°N) [7498100]	• Health status • Mean age (range), y • Male (%)	No HTN 70 (63–76) 46%	25(OH)D: 34.5 nmol/L (treatment group), 32.25 nmol/L (control group)	Vit D_3 100,000 IU (2.5 mg) one-time dose vs. Placebo	nd	Complete trial performed in winter
Pfeifer 2001[238] Lower Saxony, Germany (52°N) [11297596]	• Health status • Mean age (range), y • Male (%)	Healthy, low Vit D 75 (70–86) 0	25(OH)D < 50 nmol/L	Vit D_3 + Ca supplement vs. Ca supplement	95±12% for the Ca tablets and 96±10% for the Vit D_3 + Ca tablets (pill counting)	
Nagpal 2009[96] New Delhi, India (28.5°N) [19125756]	• Health status • Mean age (SD), y • Male (%)	Healthy, obese 44 (8) 100%	25(OH)D: 36.5 nmol/L (treatment group), 30.0 nmol/L (control group)	Vit D_3 120,000 IU every 2 weeks vs. Placebo	100% (implied); supervised home visits	Excluded subjects who refused subsequent blood draws

Table 42. Vitamin D and blood pressure: Characteristics of RCTs (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
NEW Studies						
Forman 2013[227] Boston, MA	• Health status • Mean age (range), y • Male (%)	Healthy 51 (44–59) 34.6%	Serum vitamin D- 39.3 (26.8–83.5 IQR) nmol/L	Vit D_3 100,000 IU/day Vs. Vit D_3 2000 IU/day Vs. Vit D_3 4000 IU/day Vs. placebo	96.6%	
Gepner 2012[229] Madison, WI	• Health status • Mean age (range), y • Male (%)	Healthy Postmenopausal 63.9 (SD 3) 0%	Serum vitamin D- 78.3+/-26.5 nmol/L	Placebo Vs. Vit D_3 2500 IU/day	nd	
Jorde 2010[230] Norway	• Health status • Mean age (SD), y • Male (%)	Using blood pressure or lipid lowering medication Overweight/Obese 47.5 (SD 11.4) 35.8%	58.0 ± 21.1 nmol/L	DD (40,000 IU Vit D_3/week)+500 mg calcium/day Vs. DP (20,000 IU Vit D_3/week)+500 mg calcium/day Vs. PP (placebo)+500 mg calcium/day	Vitamin D/ placebo capsules 95%-DD group, 96%-DP group and 96%-PP group calcium tablets 82%, 84% and 83%,respectively.	
Wood 2012[231] Aberdeen, UK	• Health status • Mean age (range), y • Male (%)	Healthy Post-menopausal 63.9 (SD 2.3) 0%	Serum 25(OH)D placebo: 36.18 ± 17.1 nmol/l 400 IU D3 group: 32.74 ± 12.9 nmol/l 1000 IU D3 group: 32.41 ± 13.8 nmol/l	400 IU Vit D/day Vs. placebo	nd	

Table 42. Vitamin D and blood pressure: Characteristics of RCTs (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Zhu 2013[232] Shanghai, China	• Health status • Mean age (range), y • Male (%)	Healthy 20.3 (SD 0.8) 14.3%	Habitual Ca intake CaD group—426.5 +/- 152.2 mg/d Control group—392.1 +/- 141.1 mg/d	(energy-restricted diet+600 mg calcium+125 IU Vit D)/day Vs. energy-restricted diet alone (control)	95.8% in the calcium+D group	
Daly 2009[233] Melbourne, Australia	• Health status • Mean age (SD), y • Male (%)	Healthy, obese 61.2 (SD 7.5) 100%	Serum 25(OH)D milk group: 78 ± 23 nmol/l control group: 76 ± 23 nmol/l	(400 ml reduced fact milk fortified with 1000 mg calcium+800 IU Vit D)/day Vs. control (no additional fortified milk) (400 ml reduced fact milk fortified with 1000 mg clacium+800 IU Vit D)/day Vs. control (no additional fortified milk)	85 ± 21%	
Salehpour 2012[234] Tehran, Iran	• Health status • Mean age (SD), y • Male (%)	Overweight, obese 38 (SD 8.1) 0%	Serum 25(OH)D Vit D group—36.8 +/- 30 nmol/l Placebo group—46.9 +/- 32 nmol/l	Vit D 25 µg/day Vs. placebo	nd	
Witham 2013[235] UK	• Health status • Mean age (SD), y • Male (%)	Healthy 39.4 (SD 11.8) 0%	<50 nmol/L	Vit d3 100,000 units Vs. placebo	nd	

Table 42. Vitamin D and blood pressure: Characteristics of RCTs (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Toxqui 2013[228] Spain	• Health status • Mean age (SD), y • Male (%)	Healthy 26.5 (SD 3.8) 0%	Serum: D-placebo 62.9 ± 20.8 nmol/L D-fortified 62.3 ± 20.8 nmol/L	vit d 200 IU/day Vs. placebo	>96%	
Wamberg 2013[236]	• Health status • Mean age (SD), y • Male (%)	Overweight/obese 41.2 (18–50) (SD 6.8) 27%	34.6±10.3 nmol/L	7000 IU cholecalciferol vs. placebo	94±8%	

Table 43. Vitamin D and blood pressure: Results of RCTs

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
SYSTOLIC BLOOD PRESSURE														
Scragg 1995[237] UK [7498100]	63–76 y, Both	SBP	1°	5 wk	Vit D_3 100,000 IU (2.5 mg), 1 dose	95	mm Hg	149	-5	-14.4, 4.4[A]	0	-4.2, 4.2[A]	0.81	A
					Placebo	94		147	-5	-17.9, 7.9[A]				
Pfeifer 2001[238] Germany [11297596]	70–86 y, Women	SBP	1°	8 wk	Vit D_3 800 IU +Ca carbonate 1200 mg	73	mm Hg	144.1	-13.1	nd	-7.4	-13.6, -1.2[A]	0.02	B
					Ca carbonate 1200 mg	72		140.6	-5.7	nd				
Nagpal 2009[96] New Delhi, India [19125756]	44 (8, SD) Men	SBP	2°	6 wk	Vit D_3 120,000 IU every 2 wk	35	mm Hg	124	0.6	-2.7, 3.9	4	-0.02, 8.0	0.06	B
					Placebo	36		124	-3.4	-5.8, -1.0				

Table 43. Vitamin D and blood pressure: Results of RCTs (continued)

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
DIASTOLIC BLOOD PRESSURE														
Scragg 1995[237] UK [7498100]	63–76 y, Both	DBP	1°	5 wk	Vit D_3 100,000 IU (2.5 mg), 1 dose	95	mm Hg	82	-1	-6.8, 4.8[A]	0	-2.8, 2.8[A]	0.92	A
					Placebo	94		82	-1	-6.8, 4.8[A]				
Pfeifer 2001[238] Germany [11297596]	70–86 y, Women	SBP	1°	8 wk	Vit D_3 800 IU +Ca carbonate 1200 mg	73	mm Hg	84.7	-7.2	nd	-0.3	-0.7, -0.1[A]	0.1	B
					Ca carbonate 1200 mg	72		82.6	6.9	nd				
Nagpal 2009[96] New Delhi, India [19125756]	44 (8, SD) Men	SBP	2°	6 wk	Vit D_3 120,000 IU every 2 wk	35	mm Hg	78	0.4	-2.1, 3.0	1.7	-1.5, 4.9	0.31	B
					Placebo	36		77	-1.3	-3.2, 0.7				

Table 43. Vitamin D and blood pressure: Results of RCTs (continued)

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
NEW Studies														
Forman 2013[227] Boston, MA	19–50 yrs	DBP	1°	3 months	Vit D_3 1000 IU/day	68	mmHg	79.8	final= 78.0	se=1.6	-0.9[B]	-5.7, 3.9	0.71	A
					Vit D_3 2000 IU/day	73		77.6	final= 76.0	se=1.8	-2.9[B]	-7.9, 2.1	0.26	
					Vit D_3 4000 IU/day	70		79.8	final= 78.0	se=1.6	-0.9[B]	-5.7, 3.9	0.71	
					placebo	72		78	final= 78.9	se=1.8				
		SBP			Vit D_3 1000 IU/day	68		124.7	final= 122.5	se=2.0	-2.4[B]	-8.6, 3.8	0.45	
					Vit D_3 2000 IU/day	73		122.8	final= 120.0	se=2.4	-4.9[B]	-11.6, 1.8	0.15	
					Vit D_3 4000 IU/day	70		130.4	final= 126.6	se=2.6	+1.7[B]	-5.3, 8.7	0.63	
					placebo	72		122.2	final= 124.9	se=2.4				
Gepner 2012[229] Madison, WI	Post-menopause	brachial DBP	2°	4 months	placebo	57	mmHg	72.6	change= -0.4	sd=4.4				A
		brachial DBP			Vit D_3 2500 IU/day	57		72.45	change= -0.7	sd=5.1	-0.3	-2.1, 1.5	0.73	
		brachial SBP			placebo	57		122.2	change= -2.5	sd=10.9				
		brachial SBP			Vit D_3 2500 IU/day	57		122.3	change= -0.3	sd=8.4	+2.2	-1.4, 5.8	0.23	
		central DBP			placebo	57		73.7	change= -0.5	sd=4.4				
		central DBP			Vit D_3 2500 IU/day	57		73.5	change= -0.7	sd=5.1	-0.2	-2.0, 1.6	0.82	
		central SBP			placebo	57		115.6	change= -2.1	sd=9.7				
		central SBP			Vit D_3 2500 IU/day	57		116.7	change= -0.3	sd=7.0	+1.8	-1.3, 4.9	0.26	

Table 43. Vitamin D and blood pressure: Results of RCTs (continued)

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	nterventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Jorde 2010[230] Norway	19–50, 51–70 yrs	DBP	1°	1 yr	DD (40,000 IU Vit D_3/week)+500 mg calcium/day	114	mmHg	76.5	change=1.0	sd=7.4	+0.8	-1.3, 2.9	0.45	B
		DBP			DP (20,000 IU Vit D_3/week)+500 mg calcium/day	104		74.9	change=1.0	sd=8.3	+0.8	-1.4, 3.0	0.48	
		DBP			PP (placebo)+500 mg calcium/day	112		74.8	change=0.2	sd=8.3				
		SBP			DD (40,000 IU Vit D_3/week)+500 mg calcium/day	114		124	change=1.2	sd=11.4	+2.3	-0.9, 5.5	0.15	
		SBP			DP (20,000 IU Vit D_3/week)+500 mg calcium/day	104		121	change=3.5	sd=11.8	+4.6	1.3, 7.9	<0.001	
		SBP			PP (placebo)+500 mg calcium/day	112		125	change= -1.1	sd=12.8				
Wood 2012[231] Aberdeen, UK	Post-menopause	DBP	1°	1 yr	400 IU Vit D/day	97	mmHg	77.68	change= -2.5	-3.6, -1.4	-0.4	-1.9, 1.1	0.60	A
		DBP			placebo	100		77.7	change= -2.1	-3.1, -1.0				
		SBP			400 IU Vit D/day	96		128.16	change= -2.2	-3.3, -0.7	+0.2	-2.2, 2.6	0.87	
		SBP			placebo	98		128.18	change= -2.4	-4.5, -0.2				

Table 43. Vitamin D and blood pressure: Results of RCTs (continued)

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	nterventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Zhu 2013[232] Shanghai, China														
		DBP	1°	12 weeks	(energy-restricted diet+600 mg calcium+125 IU Vit D)/day	22	mmHg	70.7	final= 64.2	sd=4.7	-1.2	-4.6, 2.2	0.48	
	19–50 yrs	DBP			energy-restricted diet alone (control)	21		70	final= 65.4	sd=6.3				B
		SBP			(energy-restricted diet+600 mg calcium+125 IU Vit D)/day	22		119.2	final= 109.6	sd=9.9	-2.3	-8.6, 4.0	0.46	
		SBP			energy-restricted diet alone (control)	21		123	final= 111.9	sd=10.4				
Daly 2009[233] Melbourne, Australia														
		DBP	1°	2 yrs	(400 ml reduced fact milk fortified with 1000 mg calcium+800 IU Vit D)/day	66	mmHg	69.5	change=4.2	2.1, 6.2	+0.3	-2.6, 3.2	0.84	
	51–70 yrs	DBP			control (no additional fortified milk)	58		71	change=3.9	2.0, 5.8				A
		SBP			(400 ml reduced fact milk fortified with 1000 mg clacium+800 IU Vit D)/day	66		123.7	change=6.8	4.2, 9.3	+1.5	-2.4, 5.4	0.45	
		SBP			control (no additional fortified milk)	58		120.4	change=5.3	2.4, 8.2				

Note: Outcomes cells are shaded for the Control rows.
[A]Estimated from available data; [B] Estimated net difference and p-value from data

Vitamin D and Bone Mineral Density or Bone Mineral Content

The current report identified a number of RCTs that examined the effect of supplementation with vitamin D alone or vitamin D plus calcium on bone mineral density(BMD)/content (BMC), falls, and muscle strength and met criteria for inclusion. Studies that report on supplementation with vitamin D plus calcium (compared with a placebo) are described later in the report.

For bone health outcomes (e.g., bone mineral density, fracture, fall or muscle strength), **the original report** relied on a recent comprehensive systematic review performed by the Ottawa EPC (Table 28).[8] Because the Ottawa's EPC report did not have separate analyses on the effect of vitamin D supplementation alone, the results for the effect of vitamin D alone or in combination with calcium supplementation are presented in "Combined vitamin D and Calcium" section.

The Ottawa EPC report was updated with literature published between January 2006 and September 2008, selected according to our eligibility criteria. For adults, only bone mineral density (BMD) indices were included. For children, only bone mineral content (BMC) indices were included. Only RCTs with duration more than 1 year qualified for inclusion.

Synopsis

Eight studies were identified for the current report that assessed the effects of supplemental vitamin D on bone mineral content or density. Of the seven studies, a study in infants and a study in postmenopausal women, showed a trend toward increasing BMC or BMD, respectively.

The Ottawa EPC report concluded that observational studies suggested a correlation between higher serum 25(OH)D concentrations and larger values of BMC indices for older children and adolescents (6 months through 18 years old). Furthermore, Based on results of the observational studies, there is fair evidence to support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck in postmenopausal women and elderly men. However, there was discordance between the results from RCTs and the majority of observational studies.[8] Three new RCTs identify from our updated search all showed no significant effects of vitamin D supplementation on BMC or BMD in children or adults, respectively.

Our updated search did not identify any new RCTs examining the effect of vitamin D on BMD and related outcomes in pregnant or lactating women.

Detailed Presentation (Tables 44 & 45)

Current Report

Eight studies examined the effects of supplementation with vitamin D alone (or vitamin D plus calcium compared with calcium alone): one in infants,[239] two in adolescent girls in India[240] and Denmark and the remainder in adults.[241-245] Study duration ranged from 10 weeks (for the infants) to 2 years, with most lasting 1 year. Daily doses ranged from 200IU to 5700IU.

The study of infants (rated A), which administered doses ranging from 400IU to 1600IU daily from 2 weeks of age to 12 weeks of age observed a trend toward increasing BMC.[239] One study of adolescents (rated B) showed slightly increased BMC in girls within 2 years of menarche. And a study of 305 postmenopausal Scottish women who received 0, 400, or

1000IU/d showed decreased loss of hip but not spine BMD with 1000IU/d.[240,245] The remaining studies (one rated A, three B, one C) found no effects of vitamin D supplementation on BMD.

Ottawa EPC Report: Bone Mineral Content—Infants (0 Through 12 months)

Overall, there is inconsistent evidence for an association between a specific serum 25(OH)D concentration and the bone health outcome BMC in infants. Of the two RCTs examining BMC, one demonstrated no significant benefit of higher serum 25(OH)D concentrations on radial bone mass while the other showed a transient increase of BMC compared to the unsupplemented group at 12 weeks but not 26 weeks. Of the three case-control studies, greater whole body BMC, was related to higher serum 25(OH)D concentrations.

Ottawa EPC Report: Bone Mineral Content or Density—Older Children (6 Months Through Before Puberty) and Adolescents (Onset of Puberty Through 18 Years)

Overall, there was fair evidence of an association between 25(OH)D concentrations and baseline BMD and change in BMD or BMC indices from the studies in older children and adolescents. However, the results from two RCTs of vitamin D supplementation have not confirmed a consistent benefit on BMD or BMC across sites and age groups.

There were seven studies in older children and adolescents (two RCTs, three cohorts, one case-control and one before-after study) that evaluated the relationship between serum 25(OH)D concentrations and BMC or BMD. In older children, there was one RCT, one prospective cohort and one before-after study. One RCT did not find an association between serum 25(OH)D concentrations and distal radial BMC. Two of three studies found an association between lower baseline serum 25(OH)D concentrations and lower BMC or BMD. The effect of bone size and muscle mass on these outcomes in relation to baseline serum 25(OH)D concentrations was not reported. One RCT demonstrated a significant relation between baseline serum 25(OH)D concentrations and baseline BMD of the lumbar spine, femoral neck and radius. However, only high dose supplementation with 14,000 IU/wk of vitamin D_3 increased BMC of the total hip.

Ottawa EPC Report: Bone Mineral Density—Postmenopausal Women and Elderly Men

Overall, there was discordance between the results from RCTs and the majority of observational studies that may be due to the limitations of observational studies to control for all relevant confounders. Five RCTs, and three cohort studies did not find an association between serum 25(OH)D concentrations and BMD or bone loss. Four cohort studies found a significant association between 25(OH)D concentrations and bone loss, which was most evident at the hip sites but the evidence for an association between 25(OH)D concentrations and lumbar spine BMD was weak. Six case-control studies suggested an association between 25(OH)D concentrations and BMD and the association was most consistent at the femoral neck BMD.

Based on the results from the observational studies, there is fair evidence to support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck. Specific circulating concentrations of 25(OH)D below which bone loss at the hip was increased ranged from 30–80 nmol/L.

Ottawa EPC Report: Bone Mineral Density—Pregnant or Lactating Women

One cohort study did not find an association between serum 25(OH)D concentrations and change in BMD that occurred during lactation. Limitations in the study design and sources of bias highlight the need for additional research on vitamin D status in pregnancy and lactation, and the association with bone health outcomes.

Additional Studies Published After the Ottawa EPC Report

One A-quality RCT compared the effect of vitamin D_2 supplementation on hip BMC in 256 elderly women between 70 and 90 years of age. All elderly women in this trial had normal physical functioning. They were randomly assigned to receive either vitamin D_2 (1000 IU/d) plus calcium (1200 mg/d) supplement or calcium (1200 mg/d) supplement alone for one year. The mean baseline dietary calcium intake was 1097 mg/d and mean 25(OH)D concentration was 44.3 nmol/L. Total hip BMD increased significantly in both groups, with no difference between the vitamin D_2 plus calcium and calcium alone groups (hip BMD change: vitamin D, +0.5%; control, +0.2%).

One B quality RCT analyzed 89 and 83 healthy adult women and men separately.[246] The participants were Pakistani immigrants living in the Copenhagen area of Denmark (latitude 55 N°). Women and men were randomly assigned to receive either daily dose of 400 IU or 800 IU vitamin D_3, or placebo for one year. For women, the mean baseline dietary calcium intake was 495 mg/d and mean 25(OH)D concentration was 12 nmol/L. For men, the mean baseline dietary calcium intake was 548 mg/d and mean 25(OH)D concentration was 21 nmol/L. At the end of study, in both women and men, there were no significant differences in lumbar spine BMD changes between the two doses of vitamin D_3 (400 IU/d or 800 IU/d) and the placebo groups.

Two RCTs, both rated C, compared the effect of vitamin D supplementation on BMC in healthy girls, aged between 10 and 17 years old.[48,246] The first RCT analyzed 26 healthy girls, who were Pakistani immigrants primarily living in the Copenhagen area Denmark (latitude 55 N°).[246] Girls were randomly assigned to receive either daily dose 400 IU or 800 IU vitamin D_3, or placebo for one year. The mean baseline dietary calcium intake was 510 mg/d and mean 25(OH)D concentration was 11 nmol/L. At the end of study, there were no significant differences in whole body BMC changes between the two doses of vitamin D_3 (400 IU/d or 800 IU/d) and the placebo groups. The second RCT analyzed 168 healthy girls, living in the Greater Beirut area, Lebanon (latitude 33°N).[48] Girls were randomly assigned to receive either weekly oral vitamin D doses of 1400 IU (equivalent to 200 IU/d) or 14,000 IU (equivalent to 2000 IU/d) or placebo for one year. The mean baseline dietary calcium intake was 677 mg/d and mean 25(OH)D concentration was 35 nmol/L. At the end of study, there were no significant differences in whole body BMC changes between either low-dose vitamin D (200 IU/d) or high-dose vitamin D (2000 IU/d) and the placebo groups. The same findings were seen when analyses were restricted to either premenarchal or postmenarchal girls. Both RCTs were rated C because the results were not adjusted for important potential confounders, such as height, bone area, lean mass, sun exposure, and pubertal status.

Findings by Life Stage

- **0–6 mo**

  One study identified for the current report found a trend toward increasing BMC for infants given high-dose supplements of vitamin D. The Ottawa EPC report concluded that there is inconsistent evidence for an association between a specific serum

25(OH)D concentration and the bone health outcome BMC in infants. There were no new data since the Ottawa report.

- **7 mo–2 y**
  The Ottawa EPC report concluded that there was fair evidence of an association between 25(OH)D concentrations and baseline BMD and change in BMD or BMC indices from the studies in older children and adolescents. There were no new data since the Ottawa report.
- **3–8 y**
  The Ottawa EPC report concluded that there was fair evidence of an association between 25(OH)D concentrations and baseline BMD and change in BMD or BMC indices from the studies in older children and adolescents. There were no new data since the Ottawa report.
- **9–18 y**
  Two RCTs identified for the current report assessed the effects of vitamin D supplementation on BMC in adolescent girls: One, which administered high doses, observed a trend for girls within two years of menarche. The other saw no effects. The Ottawa EPC report concluded that there was fair evidence of an association between 25(OH)D concentrations and baseline BMD and change in BMD or BMC indices from the studies in older children and adolescents. Two new RCTs enrolled only girls in this life stage. The results showed no significant differences in whole body BMC changes between either lower doses of vitamin D (200 or 400 IU/d) or higher dose of vitamin D (800 or 2000 IU/d) and the placebo groups.
- **19–50 y**
  RCTs identified for the current report for populations of adults observed no effects of vitamin D on BMD. The Ottawa EPC report concluded that there was discordance between the results from RCTs and the majority of observational studies in postmenopausal women and elderly men. Based on results of the observational studies, there is fair evidence to support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck. One new RCT enrolled primarily men and women in this life stage. The results showed that there were no significant differences in lumbar spine BMD changes between the two doses of vitamin D_3 (400 IU/d or 800 IU/d) and the placebo groups.
- **51–70 y**
  RCTs identified for the current report for populations of adults observed no effects of vitamin D on BMD. The Ottawa EPC report concluded that there was discordance between the results from RCTs and the majority of observational studies in postmenopausal women and elderly men. Based on results of the observational studies, there is fair evidence to support an association between serum 25(OH)D and BMD or changes in BMD at the femoral neck. One new RCT enrolled some men in this life stage. The results showed that there were no significant differences in lumbar spine BMD changes between the two doses of vitamin D_3 (400 IU/d or 800 IU/d) and the placebo groups.
- **≥71 y**
  The Ottawa EPC report concluded that there was discordance between the results from RCTs and the majority of observational studies in postmenopausal women and elderly men. Based on results of the observational studies, there is fair evidence to support an

association between serum 25(OH)D and BMD or changes in BMD at the femoral neck. One new RCT enrolled only elderly women in this life stage. The results showed that vitamin D_2 supplementation (1000 IU/d) had no additional effect on hip BMD compared to calcium supplementation alone.

- **Postmenopause**
  Two RCTs of vitamin D supplementation of postmenopausal women identified for the current report found no effect. One RCT found an effect on hip BMD but not spinal BMD and only at the higher of two doses (1000IU vs. 400IU/d). There were no new data since the Ottawa report.
- **Pregnant & lactating women**
  No studies identified for the current report enrolled this population. There were no new data since the Ottawa report.

Table 44. Vitamin D and bone mineral density: Characteristics of RCTs published after the Ottawa EPC report (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Zhu 2008[247] Perth, Australia (32 °S) [18410225]	• Health status	nd (based on the inclusion and exclusion criteria, assume subjects were not very healthy but normal physical functioning)	25(OH)D: 44.3 nmol/L Ca: 1097 mg/d	Vit D_2 1000 IU/d + Ca citrate 1200 mg/d vs. Ca citrate 1200 mg/d	86.7% and 86.8% in the vitamin D and the control groups (tablet counting)	
	• Mean age (SD), y	77 (4.5)				
	• Male (%)	0				
Andersen 2008[246] Copenhagen, Denmark (55 N°) [18208636]	• Health status	Healthy	25(OH)D: Adolescent girls: 11 nmol/L Women: 12 nmol/L Men: 21 nmol/L Ca: Adolescent girls: 510 mg/d Women: 495 mg/d Men: 548 mg/d	Vit D3 400 IU/d, or Vit D3 800 IU/d vs. placebo	The median compliance was 85 (range 43–100), 92 (42–115) and 93 (33–105)% for girls, women, and men, respectively (pill counting)	Pakistani, living in Denmark. Compliance was lower for girls.
	• Mean age (range), y	Adolescent girls: 12.2 (10.1–14.7) Women: 36.2 (18.1–52.7) Men: 38.3 (17.9–63.5)				
	• Male (%)	42				
El-Hajj 2006[48] Beirut, Lebanon (33°53'N) [16278262]	• Health status	Healthy	25(OH)D: 34.9 nmol/L Ca: 677 mg/d	Weekly oral Vit D doses of 1400 IU (=Vit D 200 IU/d) or 14,000 IU (Vit D 2000 IU/d) vs. placebo	Placebo—98%, Low dose group—98%, High dose group—97% (pill counting)	
	• Mean age (range), y	13.2 (10–17)				
	• Male (%)	0				

Table 44. Vitamin D and bone mineral density: Characteristics of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
NEW Studies						
Grimnes 2012[241] Norway	• Health status • Mean age (SD), y • Male (%)	Post-menopausal 63.5 (SD 6.8) 0%	Serum vitamin D: high dose group- 70.7+/-23.0 nmol/L; standard dose group- 71.2+/-22.3 nmol/L	high dose (6500 IU/day)+1000 mg elemental calcium/day vs. standard dose(800 IU/day)+1000 mg elemental calcium/day	97% compliance	
Holmlund-Suila 2012[239] Helsinki, Finland	• Health status • Mean age (range), y • Male (%)	nd Birth 50%	53 nmol/L	Vit D_3 1600 IU/day Vs. Vit D_3 1200 IU/day Vs. Vit D_3 400 IU/day	82% compliance	.
Iuliano-Burns 2012[242] Australiano Antarctic Division	• Health status • Mean age (range), y • Male (%)	Healthy 41 (24–65) 83%	Monthly- 55+/-14 nmol/L Bi-monthly- 60+/-15 nmol/L Single dose- 63+/-12 nmol/L	monthly (Vit D_3 50,000 IU/month) vs. bimonthly (Vit D_3 50,000 IU in alternate months) vs. single dose (one does of Vit D_3 50,000 IU pre departure)		
Jorde 2010[243] nd	• Health status • Mean age (SD), y • Male (%)	Overweight/Obese 50.8 (10.7) nd	57.7 +/-20.7 nmol/L	DD (Vit D_3 40,000 IU/week+500 mg calcium Vs.) DP (Vit D_3 20,000 IU/week+500 mg calcium) Vs. PP (Placebo+500 mg calcium)	Vitamin D- DD-95%, DP-96%, PP-96%, calcium-82%, 84%, and 83%	
Khadilkar 2010[240] Pune, India	• Health status • Mean age (range), y • Male (%)	nd 14.6 (14.3–15.3) 0%	Vit D + Ca- 24.5 nmol/L (12.7–33.2) Placebo +Ca- 20.8 nmol/L (12.7–30.4)	Vit D_2 300,000 IU x 4 times/year + 250 mg elemental calcium/day Vs. Placebo x 4 times/year + 250 mg elemental calcium/day	nd	

Table 44. Vitamin D and bone mineral density: Characteristics of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Molgaard 2010[248] Copenhagen and Frederiksberg, Denmark	• Health status • Mean age (SD), y • Male (%)	Healthy 11.4 (SD 0.2) 0%	Vitamin D intake: pacebo-2.6±1.4ug/d Serum vitamin D level:placebo-43.4±17.1 nmol/L Calcium intake: placebo-955±588 mg/d	10 µg Vit D_3/day Vs. 5 µg Vit D_3/day Vs. placebo	placebo:88±12 5ug/d: 90±10 10ug/d 88±11	
Nieves 2012[244] New York, US	• Health status • Mean age (SD), y • Male (%)	Vit D deficient/depleted 61.2 (SD 7.6) 0%	Serum 25(OH)D: 29.0±14.3 nmol/L	1,000 IU Vit D_3 Vs. placebo	95%	
Macdonald 2013[245] Scotland, UK	• Health status • Mean age (SD), y • Male (%) • Health status • Mean age (SD), y • Male (%)	Healthy, post menopausal 64.6 (SD 2.3) 0%	35.8±16.4 nmol/L	Vit d3 400 IU Vs. Vit d3 1000 IU Vs. placebo	92% (range 72% to 98%)	

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base-line	Change/ Final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Zhu 2008[247] Perth, Australia (32°S) [18410225]	71+. Women only	Hip BMD	1°	12	Vit D_2 1000 IU + Ca citrate 1200 mg	123	mg/cm^2	851	0.50%	-0.09, 1.09	0.30%	nd	NS	A
					Ca citrate 1200 mg	133		826	0.20%	-0.19, 0.59				
Andersen 2008[246] Copenhagen, Denmark (55°N) [18208636]	18–53, Women only	Lumbar spine BMD	1°	12	Vit D_3 400	30/21[A]	mg/cm^2	1.06	0%	nd	-1%	nd	NS	B
					Vit D_3 800	30/21		0.98	1%	nd	0%	nd	NS	
					Placebo	29/18		0.99	1%	nd				
Andersen 2008[246] Copenhagen, Denmark (55°N) [18208636]	18–64, Men only	Lumbar spine BMD	1°	12	Vit D_3 400	25/19[A]	mg/cm^2	1.03	2%	nd	0%	nd	NS	B
					Vit D_3 800	31/26		0.92	7%	nd	5%	nd	NS	
					Placebo	27/19		1.03	2%	nd				
Andersen 2008[246] Copenhagen, Denmark (55°N) [18208636]	10–15 y girls	BMC	1°	12	Vit D_3 400	9/7[A]	kg	1.3	22%	nd	7%	nd	NS	C[B]
					Vit D_3 800	7-Sep		1.5	10%	nd	-5%	nd	NS	
					Placebo	7-Aug		1.7	15%	nd				
El-Hajj 2006[48] Beirut, Lebanon (33°N) [16278262]	10–17 y girls	BMC	1°	12	Vit D 2000 IU	55	kg	1.2	6.20%	4.7, 7.7	0.10%	-1.1, 2.0[C]	NS	C
					Vit D 200 IU	58		1.1	6.10%	4.6, 7.6	1.10%	-0.8, 3.2[C]	NS	
					Placebo	55		1.1	5.00%	3.8, 6.2				
	Subgroup–Pre-menarchal girls, mean age 10 y	BMC	1°	12	Vit D 2000 IU	14	kg	0.8	11.60%	9.4, 13.8	4.20%	0.7, 7.7[C]	NS	
					Vit D 200 IU	12		0.7	11.40%	9.1, 13.7	4.00%	0.5, 7.5[C]	NS	
					Placebo	8		0.8	7.40%	4.7, 10.1				

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base-line	Change/ Final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
NEW Studies														
Grimnes 2012[241] Norway	Postmeno-pause	Total hip BMD	1°	1 yr	high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm^2	0.79	change=0 .31	sd=1.59	-0.25	-0.63, 0.13	0.19	A
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm^2	0.791	change=0 .56	sd=1.70				
		Femoral neck BMD			high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm^2	0.758	change=0 .03	sd=2.08	-0.14	-0.59, 0.31	0.86	
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm^2	0.757	change=0 .17	sd=1.87				
		L2-L4 BMD			high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm^2	0.901	change=0 .25	sd=3.19	-0.07	-0.80, 0.66	0.85	
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm^2	0.902	change=0 .32	sd=3.23				
		Total Body BMD			high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm^2	1	change=0 .18	sd=1.14	-0.02	-0.29, 0.25	0.88	
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm^2	1.002	change=0 .20	sd=1.23				
Holmlund-Suila 2012[239] Helsinki, Finland	0–6 mos	cortical bone density	2°	10 week (age of 3 months)	Vit D_3 1600 IU/day	29	g/cm^3	NR	final=716	se=7	-8	-12.1,-3.9	<0.001	A
					Vit D_3 1200 IU/day	28		NR	final=726	se=7	+2	-2.1, 6.1	0.34	
					Vit D_3 400 IU/day	25		NR	final=724	se=8				
		total and trabecular bone density			Vit D_3 1600 IU/day	29		NR	final=430	se=12	-18	-25, -11	<0.001	
					Vit D_3 1200 IU/day	28		NR	final=451	se=12	+3	-4, 10	0.39	
					Vit D_3 400 IU/day	25		NR	final=448	se=13				

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base-line	Change/ Final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Iuliano-Burns 2012[242] Australian Antarctic Division	19–50, 0–70 yrs	Femoral neck BMD	1°	up to 12 months (end of expedition)	monthly (Vit D_3 50,000 IU/month)	36	g/cm^2	0.86	final= 0.85	sd=0.13	-0.06	-0.12, 0	0.06	B
					bimonthly (Vit D_3 50,000 IU in alternate months)	35		0.82	final= 0.82	sd=0.10	-0.09	-0.15, -0.03	<0.001	
					single dose (one dose of Vit D_3 50,000 IU pre departure)	31		0.9	final= 0.91	sd=0.13				
		Lumbar spine (L1-L4) BMD			monthly (Vit D_3 50,000 IU/month)	36		1	final= 0.98	sd=0.16	-0.09	-0.17, -0.01	0.03	
					bimonthly (Vit D_3 50,000 IU in alternate months)	35		1	final= 1.00	sd=0.09	-0.07	-0.14, -0.0	0.05	
					single dose (one dose of Vit D_3 50,000 IU pre departure)	31		1.08	final= 1.07	sd=0.18				
		Total proximal femur BMD			monthly (Vit D_3 50,000 IU/month)	36		1.02	final= 0.85	sd=0.13	-0.23	-0.30, -0.16	<0.001	
					bimonthly (Vit D_3 50,000 IU in alternate months)	35		1.01	final= 1.01	sd=0.08	-0.07	-0.13, -0.01	0.02	
					single dose (one dose of Vit D_3 50,000 IU pre departure)	31		1.08	final= 1.08	sd=0.15				

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base-line	Change/ Final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Jorde 2010[243] nd	19–50, 51–70 yrs	BMD L2-L4	1°	1 yr	DD (Vit D_3 40,000 IU/week+500 mg calcium)	110	g/cm^2	1.27	change=0.008	sd=0.036	+0.00	-0.01, 0.01	0.85	B
					DP (Vit D_3 20,000 IU/week+500 mg calcium)	97		1.235	change=0.008	sd=0.039	+0.01	0.0, 0.01	0.86	
					PP (Placebo+500 mg calcium)	105		1.251	change=0.007	sd=0.042				
		BMD total hip			DD (Vit D_3 40,000 IU/week+500 mg calcium)	110		1.107	change=0.008	sd=0.014	-0.00	-0.01, 0.0	0.64	
					DP (Vit D_3 20,000 IU/week+500 mg calcium)	97		1.067	change=0.011	sd=0.014	+0.0	-0.0, 0.01	0.36	
					PP (Placebo+500 mg calcium)	105		1.092	change=0.009	sd=0.017				
Khadilkar 2010[240] Pune, India	9–18 yrs	L2-L4 bone mineral apparent density	1°	1 yr	Vit D_2 300,000 IU x 4 times/year + 250 mg elemental calcium/day	25	g/cm^3	NR	change=4.2	0.6, 9.3	+0.5	NC	NC	B
					Placebo x 4 times/year + 250 mg elemental calcium/day	24	g/cm^3	NR	change=3.7	1.0, 7.7				
		L2-L4 BMC			Vit D_2 300,000 IU x 4 times/year + 250 mg elemental calcium/day	25	g	NR	change=10.5	4.6, 17.2	-0.8	NC	NC	
					Placebo x 4 times/year + 250 mg elemental calcium/day	24	g	NR	change=11.3	5.4, 18.0				
		Total BMC			Vit D_2 300,000 IU x 4 times/year + 250 mg elemental calcium/day	25	g	NR	change=10.1	6.1, 14.7	+1.9	NC	NC	
					Placebo x 4 times/year + 250 mg elemental calcium/day	24	g	NR	change=8.2	4.9, 12.6				

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base-line	Change/ Final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Molgaard 2010[248] Copenhagen and Frederiksberg, Denmark	9–18 yrs	L1-L4 BMC	1°	12 months	10 µg Vit D_3/day	74	g	28.9	final=36.3	sd=8.6	-1.2	-4.3, 1.9	0.44	B
					5 µg Vit D_3/day	73	g	29.4	final=37.6	sd=10.3	+0.1	-3.2, 3.4	0.95	
					placebo	74	g	29.2	final=37.5	sd=10.2				
		L1-L4 BMD			10 µg Vit D_3/day	74	g/cm^2	0.695	final=0.780	sd=0.113	-0.01	-0.05, 0.03	0.68	
					5 µg Vit D_3/day	73	g/cm^2	0.698	final=0.786	sd=0.115	-0.0	-0.04, 0.04	0.91	
					placebo	74	g/cm^2	0.697	final=0.788	sd=0.121				
		whole body BMD			10 µg Vit D_3/day	74	g/cm^2	0.872	final=0.917	sd=0.080	+0.01	-0.02, 0.03	0.53	
					5 µg Vit D_3/day	73	g/cm^2	0.866	final=0.915	sd=0.075	+0.01	-0.02, 0.03	0.63	
					placebo	74	g/cm^2	0.863	final=0.909	sd=0.075				
		whole body BMC			10 µg Vit D_3/day	74	g	1308	final=1561	sd=366	+38	-74, 150	0.50	
					5 µg Vit D_3/day	73	g	1311	final=1559	sd=324	+36	-70, 142	0.50	
					placebo	74	g	1277	final=1523	sd=324				
Nieves 2012[244] New York, US	Postmeno-pause	femoral neck BMD	1°	2 yrs	1,000 IU Vit D_3	55	g/cm^2	NR	change=-0.2	NR	+0.6	NC	NC	A
					placebo	48		NR	change=-0.8	NR				
		spine BMD			1,000 IU Vit D_3	55		1.154	change=-0.5	NR	+0.1	NC	NC	
					placebo	48		1.212	change=-0.6	NR				
		total hip BMD			1,000 IU Vit D_3	55		1.043	change=-0.5	NR	+0.2	NC	NC	
					placebo	48		1.04	change=-0.7	NR				
		trochanter BMD			1,000 IU Vit D_3	55		NR	change=-0.3	NR	+0.15	NC	NC	
					placebo	48		NR	change=-0.45	NR				

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report) (continued)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base-line	Change/ Final	Change/ final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Macdonald 2013[245]		total hip BMD	1°	1 yr	Vit d3 400 IU	83	g/cm2	0.917	final= 0.912	sd=0.103	-0.002	-0.036, 0.032	0.91	A
					Vit d3 1000 IU	88		0.923	final= 0.923	sd=0.135	+0.009	-0.029, 0.047	0.64	
					placebo	88		0.92	final= 0.914	sd=0.118				
		total lumbar spine BMD			Vit d3 400 IU	83		1.075	final= 1.076	sd=0.135	+0.006	-0.038, 0.050	0.79	
					Vit d3 1000 IU	88		1.068	final= 1.071	sd=0.164	+0.001	-0.046, 0.048	0.97	
					placebo	88		1.081	final= 1.070	sd=0.153				

Note: Outcomes cells are shaded for the Control rows.
[A]Baseline/final sample size
[B]Downgraded to C because very small sample size (insufficient power) and no adjustments for confounders
[C]Estimated from available data

Combined Vitamin D and Calcium and Health Outcomes

Women's Health Initiative (WHI) Trial

The WHI trial provided data for numerous health outcomes of interest. For this reason and because of some methodological issues unique to this trial, the study is discussed here. The trial compared combined vitamin D_3 400 IU and calcium carbonate 1000 mg daily versus placebo in a 7-year trial in 36,282 postmenopausal women (age 50–79 y). The Tufts EPC, members of the Technical Expert Panel, and reviewers of the draft report debated about the quality of this trial. It was generally agreed that the overall methodological rigor and analyses were of good quality for most outcomes. However, there was not complete consensus on how to regard the fact that the women in both groups of this 7-year trial were allowed to take additional vitamin D supplements up to 600 IU and later 1000 IU per day and calcium supplements up to 1000 mg per day. At baseline, about one-third of women in both supplement and placebo groups were taking vitamin D supplements of at least 400 IU/d and 29 percent were taking at least 500 mg/d of supplemental calcium; by the end of the trial 69 percent of women were taking any additional supplemental calcium. During the 7 years, only about 60 percent of women (in any given year) were taking at least 80 percent of the study pills; at the end of the trial, only 76 percent were still taking any study medications. Regarding the overall quality of the study, arguments were put forward that this was a high quality effectiveness trial (in contrast with a more standardized efficacy trial) and thus had increased relevance to the actual use of supplements, that the crossover of interventions affects the applicability more than the methodological quality, and that the trial should not be downgraded because data reporting was more complete than for most trials. However, it was the consensus among the Tufts EPC that overall, the methodological quality of the trial was B, particularly when the trial is being used to guide decisions about DRI, as opposed to decisions about whether to actively recommend supplementation for an individual woman.

Combined Vitamin D and Calcium and Growth

The current report did not consider growth as an outcome, except for prenatal growth. No new studies were identified. The original report reviewed primary studies that evaluated relationships between vitamin D and calcium and growth parameters in infants and children.

Synopsis

One C-rated nonrandomized study compared combined vitamin D (1200 IU/d) and calcium (375 mg/d) to no supplementation in women in their third trimester of pregnancy. Infants of women who received supplementation were significantly heavier at birth.

Detailed Presentation (Tables 4 & 6)

Infant 0–6 Months; 7 Months–2 Years; Pregnant or Lactating Women

The original report identified a study from India that included a nonrandomized comparison between combined vitamin D (1200 IU/d) and calcium (375 mg/d) for the expectant mothers versus no supplementation. The outcome was infant birth weight.[54] This study has already been described in the "Vitamin D and Growth" section, as it also included a vitamin D only intervention arm. The study included expectant mothers with daily milk intake less than 500 mL

and estimated daily vitamin D intake less than 30 IU. It was rated C for methodological quality, because of the lack of randomization and incomplete reporting of analyses. According to the reported analysis, infants of women who received supplementation were significantly heavier at birth by 160 g on average (95% CI 0, 320).

Findings by Life Stage

- **0–6 mo**
  One C-rated nonrandomized study from India compared combined vitamin D (1200 IU/d) and calcium (375 mg/d) to no supplementation in women in their third trimester of pregnancy. Infants of women who received supplementation were significantly heavier at birth by 160 g on average (95% CI 0, 320). (See also the Pregnant & lactating women.)
- **7 mo–2 y**
  No identified study covered this life stage.
- **3–8 y**
  No identified study covered this life stage.
- **9–18 y**
  No identified study covered this life stage.
- **19–50 y**
  Not reviewed
- **51–70 y**
  Not reviewed
- **≥71 y**
  Not reviewed
- **Postmenopause**
  Not reviewed
- **Pregnant & lactating women**
  One C-rated nonrandomized study from India compared combined vitamin D (1200 IU/d) and calcium (375 mg/d) to no supplementation in women in their third trimester of pregnancy. Infants of women who received supplementation were significantly heavier at birth by 160 g on average (95% CI 0, 320). (See also the 0–6 mo category.)

Combined Vitamin D and Calcium and Cardiovascular Disease

Synopsis

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores or serum concentrations, and cardiovascular events. **As described in the original report**, a variety of cardiovascular events after 7 years were evaluated in the Women's Health Initiative (WHI) trial of combined daily vitamin D_3 400 IU and calcium carbonate 1000 mg versus placebo in 50 to 79 year old women. No statistically significant effect was found with combined vitamin D and calcium supplementation on any cardiovascular outcome. However, near significant associations were found for three outcomes, suggesting increased risk with supplementation for a composite cardiac outcome that included invasive cardiac interventions, invasive cardiac interventions, and transient ischemic attacks. No significant associations were found for cardiovascular death, a composite cardiac outcome (myocardial infarction or cardiac death), coronary heart disease death, myocardial infarction, hospitalization for heart failure, angina, combined stroke or transient ischemic attack, stroke alone, or cerebrovascular death.

A reassessment of the WHI Ca-D Trial data that controlled for women's use of personal dietary supplements found no effects of the intervention vitamin D and calcium supplements on risk for cardiovascular outcomes.

Detailed Presentation (Tables 46 & 47)

The original report described the findings of the WHI CaD with respect to cardiovascular outcomes. In the WHI trial, discussed above, the evaluated cardiovascular outcomes were all prespecified secondary outcomes.[249,250] On average, the women had normal blood pressure. There were no significant effects of the supplementation on any of the outcomes, though three of the outcomes did approach statistical significance suggesting increased events with supplementation: composite cardiac events (HR = 1.08 [95% CI 0.99, 1.19]), coronary artery bypass grafting or percutaneous coronary interventions (HR=1.09 [95% CI 0.98, 1.22]), and transient ischemic attacks (HR=1.16 [95% CI 0.95, 1.42]). The authors, however, concluded that calcium and vitamin D supplementation neither increased nor decreased coronary or cerebrovascular risk in generally healthy postmenopausal women. The outcomes cardiac death and stroke were evaluated by age decade. No interaction was found with age (no significant difference across age groups). A similar analysis based on total calcium intake (dietary plus supplemental) also found no interaction.

A post hoc analysis of the WHI CaD Trial data was found for the current report that assessed the effects of the study intervention after controlling for women's use of personal dietary supplements. This analysis found no effects of the intervention vitamin D and calcium supplements on risk for cardiovascular outcomes among women who did not use Ca or vitamin D supplements at the start of the trial (rated A).[2]

Findings per Intake Level

No conclusions are possible about a dose effect from this single study, especially since the women were allowed to take additional concurrent calcium and vitamin D supplements. However, no interaction was found with total reported calcium intake.

Findings by Age and Sex

The study investigated postmenopausal women 50 to 79 years old. No interaction of effects with decade of age was found.

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  Not reviewed
- **19–50 y**
  No data available
- **51–70 y**
  One large trial that included women mostly within this life stage (WHI) found no

significant effect of combined vitamin D_3 (400 IU) and calcium carbonate (1000 mg) on cardiovascular outcomes after 7 years.

- **≥71 y**
  Inadequate available data.
- **Postmenopause**
  All women in the WHI trial were postmenopausal. See 51–71 y life stage.
- **Pregnant & lactating women**
  Not reviewed

Table 46. Combined vitamin D and calcium and cardiovascular outcomes: Characteristics of RCTs (formerly Table 85) (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Hsia 2007[249] LaCroix 2009[250] WHI US (various) [17309935 19221190]	• Health status • Mean age (range), y • Male (%)	Any 62 (50-79) 0	Ca: 1148 (654) mg/d in treatment group; 1154 (658) in placebo group Low Ca intake (<800 mg/day): 34%	Combined Vit D & Ca supplement vs. Placebo	See discussion of use of personal supplements in the WHI trial in "Colorectal Cancer, Detailed Presentation"	
NEW Studies						
Prentice 2013[2] WHI US (various)	• Health status • Mean age (range), y • Male (%)	Post-menopausal 50–54: 14.2% (50-79) 0%	nd	1000mg/day of Ca & 400IU/day of Vit D3 Vs. placebo	nd	

Table 47. Combined vitamin D and calcium and cardiovascular outcomes: Results of RCTs (formerly Table 86) (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, y	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Hsia 2007[249] LaCroix 2009[250] WHI [17309935] [19221190]	50–79 y, Women	Cardiovascular death	2°	7	Vit D + Ca	226	18,176	HR (Suppl/Placebo)	0.92*	0.77, 1.10	NS	B
					Placebo	244	18,106					
		Cardiac composite (MI, CHD death, CABG, or PCI)	2°		Vit D_3 400 IU + Ca carbonate 1000 mg	920	18,176	HR	1.08	0.99, 1.19	0.1	
					Placebo	841	18,106					
		Cardiac composite (MI or CHD death)	2°		Vit D + Ca	499	18,176	HR	1.04	0.92, 1.18	0.5	
					Placebo	475	18,106					
		CHD death	2°		Vit D + Ca	130	18,176	HR	1.01*	0.79, 1.29	0.92	
					Placebo	128	18,106					
		MI	2°		Vit D + Ca	411	18,176	HR	1.05	0.91, 1.20	0.52	
					Placebo	390	18,106					
		CABG or PCI	2°		Vit D + Ca	674	18,176	HR	1.09	0.98, 1.22	0.12	
					Placebo	607	18,106					
		Hospitalized for heart failure	2°		Vit D + Ca	394	18,176	HR	0.95	0.83, 1.10	0.5	
					Placebo	407	18,106					
		Angina	2°		Vit D + Ca	404	18,176	HR	1.08	0.94, 1.24	0.3	
					Placebo	377	18,106					
		Cerebrovascular composite (Stroke or TIA)	2°		Vit D + Ca	563	18,176	HR	1.02	0.91, 1.15	0.75	
					Placebo	547	18,106					
		Stroke	2°		Vit D + Ca	362	18,176	HR	0.95	0.82, 1.10	0.51	
					Placebo	377	18,106					
		TIA	2°		Vit D + Ca	213	18,176	HR	1.16	0.95, 1.42	0.13	
					Placebo	182	18,106					
		Cerebrovascular death	2°		Vit D + Ca	213	18,176	HR	0.89*	0.62, 1.29	NS	
					Placebo	182	18,106					

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, y	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
New studies												
Prentice 2013[2] WHI US (various)		Primary - MI	1°	7	1000mg/day of Ca & 400IU/day of Vit D3	193	7,718	HR	1.18	0.88, 1.59	0.17	A
					placebo	167	7,584		1.00	**Reference**		
		Primary - Coronary heart disease	1°		1000mg/day of Ca & 400IU/day of Vit D3	229	7,718	HR	1.08	0.82, 1.42	0.4	
					placebo	211	7,584		1.00	**Reference**		
		Primary - Total heart disease	1°		1000mg/day of Ca & 400IU/day of Vit D3	621	7,718	HR	1.00	0.86, 1.18	0.56	
					placebo	642	7,584		1.00	**Reference**		
		Primary - Stroke	1°		1000mg/day of Ca & 400IU/day of Vit D3	184	7,718	HR	1.18	0.86, 1.62	0.96	
					placebo	162	7,584		1.00	**Reference**		
		Primary - Total cardiovascular disease	1°		1000mg/day of Ca & 400IU/day of Vit D3	848	7,718	HR	1.04	0.90, 1.19	0.77	
					placebo	813	7,584		1.00	**Reference**		

Note: Outcomes cells are shaded for the Control rows.

Combined Vitamin D and Calcium and Body Weight

The current report did not consider the topic of body weight. The original report searched for systematic reviews and primary studies that evaluated associations between combined vitamin D and calcium and *incidence of overweight or obesity*; no such studies were found. For the outcome *weight change* (in kilograms or body mass index units), **that report** included only randomized controlled trials. The EPC and the TEP agreed that the limited resources would not be expended on reviewing observational studies for the surrogate outcome body weight (where overweight or obesity are considered to be the clinical outcomes). We included only studies of adults. Studies of weight gain in children are included in the "Growth" section.

Synopsis

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and body weight in adults. One RCT each tested the effect of combined vitamin D and calcium in the setting of either an isocaloric diet or an energy restricted diet. Both used vitamin D_2 400 IU/d and calcium carbonate (one 1000 mg/d, one 1200 mg/d) and were restricted to women. In the WHI trial of postmenopausal women on an isocaloric diet after 7 years, there was a statistically significant 0.1 kg smaller weight gain in those assigned to the supplement. The effect was statistically similar across age groups. In a Quebec study of 63 overweight premenopausal women, the apparent effect of supplementation in the setting of an energy restricted diet was greater than the WHI trial (net change −1.0 kg), but this was not a significant difference between the supplement and placebo groups.

Detailed Presentation (Tables 48 & 49)

Isocaloric Diet

The WHI trial was analyzed for the effect of daily combined vitamin D_2 400 IU and calcium carbonate 1000 mg on weight.[251] The trial included about 36,000 postmenopausal women aged 50 to 79 years. The methodological quality of the study was B. At 7 year follow up, the net change in body weight (supplemented minus control) was -0.13 kg (95% CI -0.21, -0.05; less weight gained in supplement group). This was of questionable clinical significance, but was statistically significant. The investigators performed numerous subgroup analyses including those based on age. There were no substantive or statistically significant differences among the evaluated age subgroups.

Energy Restricted Diet

A trial performed in Quebec City analyzed 63 premenopausal overweight or obese women (mean age 43) comparing daily vitamin D_2 400 IU and calcium carbonate 1200 mg versus placebo.[252] Women in both study groups were placed on a weight-loss intervention which consisted of a 700 Kcal/day decrease in energy intake for 15 weeks; the women met biweekly with a nutritionist. The trial was rated methodological quality C due to a high dropout rate (25 percent) and poor description of the methodology. Women in both study groups on average lost weight, with those in the supplement group losing 1.0 kg more (4 vs. 3 kg). However, this effect was not statistically significant (P=0.19).

Findings per Vitamin D and Calcium Dose

No conclusion could be reached about a possible effect of vitamin D and calcium dose.

Findings per Age and Sex

The trials included only women. The effect of supplementation on postmenopausal women not on an energy restricted diet was of questionable clinical significance after 7 years. The effect of supplementation for 15 weeks on overweight and obese premenopausal women (in an approximate age range of 32 to 54 years) on an energy restricted diet was relatively large (-4 vs. -3 kg), but this difference between the supplemented and control groups was not statistically significant.

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  Not reviewed
- **19–50 y**
  A single trial of women on an energy restricted diet found a nonsignificant difference in weight loss between that those assigned to vitamin D 300 IU and calcium 1200 mg supplementation for 15 weeks.
- **51–70 y**
  The WHI trial found no clinically significant effect on weight of vitamin D 300 IU and calcium 1000 mg after 7 years.
- **≥71 y**
  The subgroup of women in the WHI trial in this life stage had a similar net weight change as all the study participants as a whole, but the effect was not statistically significant.
- **Postmenopause**
  All the women in the WHI trial were postmenopausal.
- **Pregnant & lactating women**
  Not reviewed

Table 48. Combined vitamin D and calcium and weight: Characteristics of RCTs (formerly Table 87) (no new studies in the current report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Caan 2007[251] WHI US (various) [17502530]	• Health status • Mean age (range), y • Male (%)	All, post-menopause 62 (50-79) 0	Ca: 1148 (654) mg/d in treatment group; 1154 (658) in placebo group	Vit D & Ca carbonate vs. Placebo	See discussion of use of personal supplements in the WHI trial in "Colorectal Cancer, Detailed Presentation"	Factorial design with HT vs. Placebo
Major 2007[252] Quebec City, Canada (47°N) [17209177]	• Health status • Mean age (range/SD), y • Male (%)	Overweight, healthy, pre-menopause 43 (5.5) 0	Ca 704 mg/d	Vit D + Ca carbonate vs. Placebo	nd	Energy restriction

Table 49. Combined vitamin D and calcium and weight: Results of RCTs (formerly Table 88) [no new studies in the current report]

Author Year Study Name [PMID]	Age Range, Sex (Subgroup)	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Isocaloric Diet														
Caan 2007[251] WHI [17502530]	50–79 y, Women	Weight	2°	7 y	Vit D_2 400 IU + Ca carbonate 1000 mg	18,129	kg	76.0	nd	nd	-0.13	-0.21, -0.05	.001[A]	B
					Placebo	18,055		75.9	nd	nd				
	(50-54 y)				Vit D_3 + Ca	2592	kg	nd	nd		-0.24	-0.45, -0.03	<0.05[B]	
					Placebo	2561		nd	nd					
	(55-59 y)				Vit D_3 + Ca	4134	kg	nd	nd		-0.08	-0.24, +0.09	NS	
					Placebo	4135		nd	nd					
	(60-69 y)				Vit D_3 + Ca	8276	kg	nd	nd		-0.15	-0.27, -0.03	<0.05	
					Placebo	8243		nd	nd					
	(70-79 y)				Vit D_3 + Ca	3174	kg	nd	nd		-0.10	-0.27, +0.09	NS	
					Placebo	2561		nd	nd					
	(White)				Vit D_3 + Ca	15,047	kg	nd	nd		-0.13	-0.22, -0.04	<0.05[C]	
					Placebo	15,106		nd	nd					
	(Black)				Vit D_3 + Ca	1682	kg	nd	nd		-0.32	-0.59, -0.06	<0.05	
					Placebo	1635		nd	nd					
	(Hispanic)				Vit D_3 + Ca	789	kg	nd	nd		-0.08	-0.48, +0.32	NS	
					Placebo	718		nd	nd					
	(Asian / Pacific Islander)				Vit D_3 + Ca	369	kg	nd	nd		+0.19	-0.37, +0.75	NS	
					Placebo	353		nd	nd					
Energy Restricted Diet														
Major 2007[252] Quebec City, Canada [17209177]	43 (SD)	Weight	2°	15 wk	Vit D_2 400 IU + Ca carbonate 1200 mg	30	kg	81.5	-4.0	+-9.0	-1.0	-2.31. +0.31	0.19	C
					Placebo	33		83.6	-3.0	+-11.7				

Note: Outcomes cells are shaded for the Control rows

[A] In addition, subgroup analyses by baseline BMI and baseline dietary calcium intake are reported.

[B] No statistically significant interaction with age.

[C] No statistically significant interaction with ethnicity.

Combined Vitamin D and Calcium and Cancer

This section explores cancer from all causes and total cancer mortality.

Synopsis

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and total cancer incidence or mortality. Two RCTs reported different effects of combined vitamin D_3 and calcium supplementation on the risk of total cancer. The WHI showed no effects,[131] while the trial conducted in Nebraska (latitude 41°N) reported significant reduction of risk of total cancer.[102] However, both vitamin D doses and baseline vitamin D status were substantially different between these two RCTs. Therefore, the effects from these two RCTs were not comparable.

Detailed Presentation (Tables 50 & 51)

The 7-year WHI trial that enrolled 36,282 postmenopausal women across the United States compared a daily supplement of vitamin D_3 (400 IU) and elemental calcium (1000 mg) with placebo and evaluated incidence of total cancer and total cancer mortality as part of multiple secondary analyses.[131] The median serum 25(OH)D level of the study population was 42 nmol/L. The trial did not find significant effect of combined vitamin D_3 and calcium supplementation on either the risk of total cancer (adjusted HR: 0.98, 95% CI 0.91, 1.05) or total cancer mortality (adjusted HR: 0.89, 95% CI 0.77, 1.03). The methodological quality of this study was rated B.

A 4-year population-based RCT[102] sampled from a 9-county, largely rural area in eastern Nebraska (latitude 41°N), aimed to determine the efficacy of vitamin D_3 (1000 IU/d) plus calcium (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d), or calcium alone (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d), compared to placebo in reducing the incidence of fracture. Incidence of cancer was a secondary outcome in this trial. A total of 734 postmenopausal women, aged more than 55 years old, were analyzed for the effect of vitamin D_3 (1000 IU/d) plus calcium (either calcium citrate 1400 mg/d or calcium carbonate 1500 mg/d). The mean 25(OH)D concentration at baseline was 72 nmol/L. Compared to the placebo group, the relative risk of developing cancer at the end of study was 0.40 (95% CI 0.20, 0.82; P=0.013) for the vitamin D_3 plus calcium group. On the hypothesis that cancers diagnosed early in the study would have been present, although unrecognized at entry, the analyses were restricted to women who were free of cancer at 1 year intervention. The relative risk of developing cancer at the end of study for the vitamin D_3 plus calcium group changed to 0.23 (95% CI 0.09, 0.60; P= 0.005). The methodological quality of this study was rated B.

Findings by Life Stage

- **0–6 mo**
  No data
- **7 mo–2 y**
  No data
- **3–8 y**
  No data
- **9–18 y**
  No data

- **19–50 y**
  No data
- **51–70 y**
  No data
- **≥71 y**
  No data
- **Postmenopause**
  The WHI trial using vitamin D_3 400 IU/d plus calcium carbonate 1000 mg/d showed no effects, while the trial in Nebraska using vitamin D_3 1000 IU/d plus calcium citrate or carbonate 1500 mg/d showed significant reduction of risk of total cancer.
- **Pregnant & lactating women**
  No Data

Table 50. Combined vitamin D and calcium and total cancer incidence: Characteristics of RCTs (formerly Table 89) (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Wactawski-Wende 2006[131] WHI US (various) [16481636]	• Health status • Mean age (range/SD), y	Post-menopausal women nd (50–79)	Ca intake (mg/d): <800, 34%; 800–200, 26%; ≥1200, 40% Median 25(OH)D: 42 nmol/L	Vit D_3 400 IU/d + Ca 1000 mg/d vs. Placebo	See discussion of use of personal supplements in the WHI trial in "Colorectal Cancer, Detailed Presentation"	
Lappe 2007[102] Nebraska, US (41º N) [17556697]	• Health status • Mean age (range/SD), y	Mentally and physically fit; post-menopause 67 (7.3)	25(OH)D: 71.8 nmol/L	Vit D_3 1000 IU/d + Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. placebo	nd	
NEW Studies						
Prentice 2013[2] WHI US (various)	• Health status • Mean age (range/SD), y	Post-menopausal women 50–54: 14.2%; 55–59: 22.8%; 60–69: 45.5%; 70–79: 17.5%; (50–79)	nd	400 IU Vit D3 + 1,000 mg elemental calcium carbonate Vs. placebo	nd	
Brunner 2011[253] WHI nd	• Health status • Mean age (range/SD), y	nd (50–79)	nd	1,000 mg elemental calcium + 400 IU of vitamin D3 Vs. placebo	nd	

Table 51. Combined vitamin D and calcium and total cancer incidence: Results of RCTs (formerly Table 90) (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Followup, year	Interventions, Daily Dose	n Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Wactawski-Wende 2006[131] WHI [16481636]	Post-menopausal women	Incident cancer (all causes)	2°	7	Vit D_3 400 IU + Ca carbonate 1000 mg	1634	18176	Adjusted HR (Vit D+Ca)/placebo	0.98	0.91, 1.05	0.53	B
					Placebo	1655	18106					
	Post-menopausal women	Total cancer mortality	2°	7	Vit D_3 400 IU + Ca carbonate 1000 mg	344	18176	Adjusted HR (Vit D+Ca)/placebo	0.89	0.77, 1.03	0.12	
					Placebo	382	18106					
Lappe 2007[102] [17556697]	Post-menopausal women	Incident cancer (all causes)	2°	4	Vit D_3 1000 IU + Ca (citrate 1400 mg or carbonate 1500 mg)	13	446	RR (Vit D+Ca)/placebo	0.4	0.20, -0.82	0.01	B
					Placebo	20	288					
	Post-menopausal women	Incident cancer (restrict to subjects who were free of cancer at 1 y intervention)	2°	4	Vit D_3 1000 IU + Ca (citrate 1400 mg or carbonate 1500 mg)	8	403	RR (Vit D+Ca)/placebo	0.23	0.09, -0.60	<0.005	
					Placebo	20	288					
NEW Studies												
Prentice 2013[2] WHI US (various)		Secondary - Total invasive cancer	1°	7.2 yrs	400 IU Vit D3 + 1,000 mg elemental calcium carbonate	553	7718	adjusted HR	0.88	0.78, 0.98	NR	A
					placebo	617	7584		1.00	**Reference**		
Brunner 2011[253] WHI nd	Post-menopausal women	Total cancer	1°	7 yrs	1,000 mg elemental calcium + 400 IU of vitamin D3	1306	18176	adjusted HR	0.98	0.90, 1.05	0.78	A
					placebo	1333	18106		1.00	**Reference**		

Note: Outcomes cells are shaded for the Control rows.

Colorectal Cancer

Synopsis

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and colorectal cancer mortality or incidence. One B quality RCT of postmenopausal women reported no significant association between supplemental vitamin D_3 and calcium and, colorectal cancer mortality or incidence.

Detailed Presentation (Tables 52 & 53)

The WHI CaD trial, **described in the original report**, compared daily supplemental vitamin D_3 (400 IU) and elemental calcium (1000 mg) with placebo in 36,282 postmenopausal women. Colorectal cancer was evaluated as a secondary endpoint.[131] The primary endpoint was the prevention of hip fracture. At 7 years vitamin D_3 and calcium supplementation had no significant effect on colorectal cancer mortality (P=0.39) or incidence (P=0.51). In a subgroup analysis, risks of colon cancer and rectal cancer were also not significantly different between the supplemented and unsupplemented groups (P=0.99 and P=0.11, respectively). This trial was rated B because it did not restrict the participants from taking personal calcium or vitamin D supplements; they had mean daily total calcium intake of 1151 mg and vitamin D intake of 367 IU at enrollment. **A post hoc analysis of the WHI CaD 7-year trial data identified for the current report compared the risk for colorectal cancer among participants who had not been taking personal calcium and vitamin D supplements at baseline with that of participants who had taken supplements; the hazard ratio for colorectal cancer risk among all participants was 1.30 (95% CI 0.88, 1.92), compared with 0.99 (95% CI 0.56, 1.77) for women who had taken no personal supplements.[2]**

Findings for Special Populations

The WHI performed 18 subgroup analyses based on baseline participant characteristics including ethnic groups, body mass index, smoking status, and geographic regions according to solar irradiance.[131] No significant interactions were found with these baseline characteristics. The same RCT with multifactorial design reported an interaction between estrogen alone or combined estrogen and progestin therapy, and combined vitamin D and calcium supplementation for colorectal cancer risk in a post hoc analysis.[254] Among women concurrently assigned to hormone replacement therapies, colorectal cancer incidence was increased in the combined supplemental vitamin D and calcium arm compared to placebo (HR 1.50, 95% CI 0.96, 2.33), whereas among those concurrently assigned to placebo in the estrogen trials, colorectal cancer risk was reduced in the vitamin D plus calcium arm compared to placebo (HR 0.71, 95% CI 0.46, 1.09) (P for interaction = 0.02).

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed

- **9–18 y**
  Not reviewed
- **19–50 y**
  No data
- **51–70 y**
  One trial that included women mostly within this life stage (WHI) found no significant association between combined vitamin D_3 (400 IU) and calcium carbonate (1000 mg) and colorectal cancer mortality or incidence.
- **71+**
  The WHI included some people within this life stage, but no study adequately evaluated this life stage.
- **Postmenopause**
  The WHI exclusively focused on postmenopausal women. The study found no association between vitamin D and calcium intake and colorectal cancer mortality or incidence.
- **Pregnant & lactating women**
  Not reviewed

Table 52. Combined vitamin D with calcium and colorectal cancer: Characteristics of RCTs (formerly Table 91) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Wactawski-Wende 2006[131] WHI US (various) [16481636]	• Health status • Mean age (range), y • Male (%)	Post-menopausal women nd (50–79) 0	Total Ca intake (mg/d) (Mean for both groups: 1151) Ca + Vit D arm: 1148 • <800: 34% • 800-<1200: 26% • ≥1200: 39% Placebo arm: 1154 • <800: 33% • 800–<1200: 26% • ≥1200: 40% Total Vit D intake (IU/d) (Mean for both groups: 367) Ca + Vit D arm: nd • <200: 38% • 200–<400: 19% • 400–<600: 23% • 600: 19% Placebo arm: nd • <200: 37% • 200–<400: 19% • 400–<600: 24% • 600: 19%	Ca 1000 mg/d + Vit D_3 400 IU/d vs. Placebo	See discussion of use of personal supplements in the WHI trial in "Colorectal Cancer, Detailed Presentation"	The outcomes were based on self-reported questionnaires. Only colorectal cancers were verified centrally. Colorectal cancer screening was not mandated in the protocol. Lost to follow up: • Ca + Vit D arm: 0.8% • Placebo arm: 0.8% Withdrawn: • Ca + Vit D arm: 1.9% • Placebo arm: 1.8%

Table 53. Combined vitamin D with calcium and colorectal cancer: Results of RCTs (formerly Table 92) [no new studies in the current report]

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, y	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Wactawski-Wende 2006[131] WHI [16481636]	Post-menopausal women	Colorectal cancer mortality	2°	7	Vit D3 400 IU + Ca carbonate 1000 mg	34	18,176	HR (Suppl/Placebo)	0.82	0.52, 1.29	0.39	B
					Placebo	41	18,106					
		Colorectal cancer	2°		Vit D + Ca	168	18,176	HR	1.08	0.86, 1.34	0.51	
					Placebo	154	18,106					
		Colon cancer	2°		Vit D + Ca	128	18,176	HR	1.00	0.78, 1.28	0.99	
					Placebo	126	18,106					
		Rectal cancer	2°		Vit D + Ca	44	18,176	HR	1.46	0.92, 2.32	0.11	
					Placebo	30	18,106					

Note: Outcomes cells are shaded for the Control rows.

Colorectal Adenoma

Synopsis

No qualified systematic reviews evaluated the association between combined vitamin D and calcium, body stores, or serum concentrations, and incidence of intestinal adenoma. One B quality RCT of postmenopausal women found no significant effect of combined vitamin D_3 and calcium supplements on the incidence of colorectal adenoma. Another B quality post hoc subgroup analysis of a secondary prevention trial of adenomatous adenoma reported that calcium supplemented patients with higher baseline 25(OH)D concentrations had significantly lower risk of relapse compared to placebo (interaction P = 0.01 between subgroups). In contrast, no significant difference in relapse rates was found in calcium supplemented patients with lower baseline 25(OH)D concentrations compared to placebo.

Detailed Presentation (Tables 52 & 53)

The WHI compared a daily supplement of vitamin D_3 (400 IU) and elemental calcium (1000 mg) with placebo and evaluated incidence of self-reported colorectal adenoma as part of multiple secondary analyses.[131] At 7 years, the incidence of adenoma was not significantly different between the supplement and placebo groups (p=0.71). All the adenoma cases were based on self-reported data, not verified by medical record review or histopathology report.

A post hoc subgroup analysis of the CPP trial of secondary adenoma prevention on the basis of calcium supplementation (1200 mg of elemental calcium) evaluated the risk of colorectal adenoma stratified by baseline 25(OH)D concentrations.[255] The primary endpoint of the original trial was the risk of recurrent adenoma. After 4 years, in the subgroup with 25(OH)D concentrations greater than 72.6 nmol/L at baseline, subjects who received supplemental calcium had a significantly lower incidence of recurrent adenoma compared to placebo (HR=0.71 [95% CI 0.57,0.89] versus HR=1.05 [95% CI 0.85, 1.29]; interaction P=0.01). In the subgroup with 25(OH)D concentrations lower than 72.6 nmol/L, the risk of recurrence was not significantly different between supplemental calcium and placebo. No subgroup data were available regarding sex, separate life stages, or other special populations (e.g., obese, smokers, ethnic groups, or users of contraceptives).

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  Not reviewed
- **19–50 y**
  The CPP included some people within this life stage, but no study adequately evaluated this life stage.
- **51–70 y**
  The analysis of the CPP with a mean age of 61 years included participants mostly within this life stage. The study found a significant association between supplemental calcium

and reduced risk of colorectal adenoma in a subgroup with 25(OH)D concentrations higher than 72.6 nmol/L.

- **71+**
  The CPP included some people within this life stage, but no study adequately evaluated this life stage.
- **Postmenopause**
  The WHI found no association between combined vitamin D_3 and calcium supplements and the incidence of colorectal adenoma.
- **Pregnant & lactating women**
  Not reviewed

Breast Cancer

Synopsis

No qualified systematic reviews evaluated the association between vitamin D and calcium intake, body stores, or serum concentrations, and breast cancer. Breast cancer incidence and breast cancer related mortality after 7 years were evaluated in the WHI CaD trial versus placebo in 50 to 79 year old women without a prior history of breast cancer, **identified for the original report**.[256] No statistically significant effect was found with combined vitamin D and calcium supplementation on incident breast cancer outcome. No significant associations were found for breast cancer related mortality.

Detailed Presentation (Tables 54 & 55)

In the WHI trial, the evaluated breast cancer incidence and breast cancer related mortality outcomes were secondary outcomes.[256] There were no significant effects of combined vitamin D and calcium supplementation on both outcomes. The authors concluded that invasive breast cancer incidence was similar in the two groups of healthy postmenopausal women: calcium and vitamin D supplementation and placebo groups. The relationship of 25(OH)D serum concentrations and the risk of breast cancer was examined in a nested case-control design. The study found no relationship between total vitamin D intake and 25(OH)D serum concentrations with the risk of breast cancer. **A post hoc analysis of the WHI CaD 7-year trial data identified for the current report compared the risk for breast cancer among participants who had not been taking personal calcium and vitamin D supplements at baseline with that of participants who had 0.89 (95% CI 0.72, 1.11), compared with 0.73 (95% CI 0.52, 1.02) for women who had taken no personal supplements, suggesting a trend toward decreased risk for breast cancer among those who did not use supplements at baseline.[2]**

Findings per Intake Level

No conclusions are possible regarding a dose effect from this single study, especially since the women in the intervention and placebo groups were allowed to take additional concurrent calcium and vitamin D supplements.

Findings by Age and Sex

The study investigated postmenopausal women 50 to 79 years old.

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  Not reviewed
- **19–50 y**
  No data available
- **51–70 y**
  The WHI trial that included women mostly within this life stage found no significant effect of combined vitamin D_3 (400 IU) and calcium carbonate (1000 mg) on incident breast cancer and mortality from breast cancer after 7 years.
- **≥71 y**
  Inadequate available data.
- **Postmenopause**
  All women in the WHI trial were postmenopausal.
- **Pregnant & lactating women**
  Not reviewed

Table 54. Combined vitamin D and calcium and breast cancer outcomes: Characteristics of RCTs (formerly Table 93) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Chlebowski 2008[256] WHI US (various) [19001601]	• Health status • Mean age (range), y • Male (%)	No breast cancer 50-79 0	Baseline Ca supplementation: Vit D & Ca arm <800: 34.3% 800–<1200: 26.5% ≥1200: 39.3% Placebo arm <800: 33.8% 800–<1200: 26.2% ≥1200: 40.0% Baseline Vit D supplementation: Vit D & Ca arm Yes: 47.1% No: 52.9% Placebo arm Yes 47. 6% No 52.4%	Combined Vit D & Ca supplement vs. Placebo	See page 242	Intervention and placebo groups were allowed to take additional concurrent calcium and vitamin D supplements.

Table 55. Combined vitamin D and calcium and breast cancer outcomes: Results of RCTs (formerly Table 94) [no new studies in the current report]

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, y	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Chlebowski 2008[256] WHI [19001601]	50–79 y, Women	Breast cancer incidence	2°	7	Vit D_3 400 IU + Ca carbonate 1000 mg	668	18176	HR (Suppl/Placebo)	0.96	0.86, 1.07	NS	B
					Placebo	693	18106					
		Death from breast cancer	2°	7	Vit D_3 400 IU + Ca carbonate 1000 mg	23	18176	HR	0.99	0.55, 1.76	NS	
					Placebo	23	18106					
		Invasive breast cancer–subgroup >67.6 baseline 25(OH)D	2°	7	Vit D_3 400 IU + Ca carbonate 1000 mg	86	195	Adj OR	0.89	0.58, 1.36	NS	
					Placebo	76	185					
		Invasive breast cancer–subgroup 55.4–<67.6 baseline 25(OH)D	2°	7	Vit D_3 + Ca	95	171	Adj OR	1.25	0.83, 1.90	NS	
					Placebo	86	171					
		Invasive breast cancer–subgroup 43.9–<55.4 baseline 25(OH)D	2°	7	Vit D_3 + Ca	102	176	Adj OR	1.07	0.70, 1.62	NS	
					Placebo	92	195					
		Invasive breast cancer–subgroup 32.4–<43.9 baseline 25(OH)D	2°	7	Vit D_3 + Ca	71	185	Adj OR	0.69	0.45, 1.06	NS	
					Placebo	102	171					
		Invasive breast cancer–subgroup <32.4 baseline 25(OH)D	2°	7	Vit D_3 + Ca	94	171	Adj OR	0.91	0.60, 1.39	NS	
					Placebo	91	176					

Note: Outcomes cells are shaded for the Control rows.

Combined Vitamin D and Calcium and Pregnancy-Related Outcomes

Preeclampsia

Synopsis

Based on data from a single RCT **identified for the original report**, there is no significant effect of combined vitamin D and calcium supplementation on the prevention of preeclampsia.

Detailed Presentation (Tables 56 & 57)

One RCT from India used a combination of vitamin D (1200 IU/d) and calcium (375 mg/d) for the prevention of preeclampsia.[257] **Table 56** describes the characteristics of the trial. The trial found no significant difference between the compared arms (**Table 57**).

Findings by Life Stage

- **0–6 mo**
  No data
- **7 mo–2 y**
  Not applicable
- **3–8 y**
  Not applicable
- **9–18 y**
  Not applicable
- **19–50 y**
  [see pregnant and lactating women]
- **51–70 y**
  Not applicable
- **71+**
  Not applicable
- **Postmenopause**
  Not applicable
- **Pregnant & lactating women**
  Based on data from a single RCT, there is no significant effect of combined vitamin D (1200 IU/d) and calcium (375 mg/d) supplementation on the prevention of preeclampsia.

Other Pregnancy-Related Outcomes

Synopsis

We did not identify any eligible studies on the relationship of vitamin D with calcium and high blood pressure, preterm birth, or small for gestational age infant.

Table 56. Combined vitamin D and calcium and preeclampsia: Characteristics of RCTs (formerly Table 95) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Marya 1987[257] India (29°N) [3623260]	• Health status • Age range, y	Any 20–35	Ca: 500 mg/d in in diet; Vit D: ~40 IU/d (unclear how it was quantified)	Combined Vit D (1200 IU/d) & Ca (375 mg/d) supplement vs. no supplement	nd	

Table 57. Combined vitamin D and calcium and preeclampsia: Results of RCTs (formerly Table 96) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, y	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Compari-son)	Result	95% CI	P Btw	Study Quality
Marya 1987[257] India (29°N) [3623260]	Pregnancy	Toxemia (preeclampsia)	1°	ND	Vit D (1200 IU) & calcium (375 mg)	12	200	RR (combined Vit D & Ca vs. nothing)	0.67	0.33, 1.35	0.26	C
					No supplement	18	200					

Note: Outcomes cells are shaded for the Control rows.

Combined Vitamin D and Calcium and Clinical Outcomes of Bone Health

Rickets, Fractures, Falls, or Performance Measures

For the current report, we identified no new studies on the effect of vitamin D and calcium supplementation on rickets that met the inclusion criteria; we identified two RCTs that assessed the effect of vitamin D and calcium supplementation on fracture risk (described in Table 59 and the accompanying text), one RCT that assessed effects on muscle strength (Table 60), and one that assessed effects on risk for falling (Table 60) (studies that assessed the effects of supplementation with vitamin D and calcium on bone mineral density or bone mineral content are described in Table 66 and the accompanying text).

For bone health outcomes (e.g., bone mineral density, fracture, fall or muscle strength), **the original report** relied on a recent comprehensive systematic review performed by the Ottawa EPC (**Table 34)**.[8] Because the Ottawa's EPC report did not have separate analyses for the effect of vitamin D supplementation alone, the results for the effect of vitamin D alone or in combination with calcium supplementation are presented in this section.

The Ottawa EPC report was updated with literature published between January 2006 and April 2009, selected according to our eligibility criteria. Only RCTs qualified for inclusion.

Synopsis

The current report identified two RCTs that found no effect of an intervention with vitamin D and calcium on osteoporotic fracture risk among postmenopausal women, one RCT of vitamin D and calcium that found no effect on muscle strength in middle-age and older men, and one RCT that found no effect on risk for falls among older women.

The Ottawa EPC report concluded that supplementation with vitamin D (most studies used D_3) plus calcium is effective in reducing fractures in institutionalized populations, but there is inconsistent evidence that supplemental vitamin D reduces falls in postmenopausal women and older men. Our update search did not identify new RCT examining the combined effect of vitamin D plus calcium supplementation on rickets, fractures, or falls in postmenopausal women and older men.

One study published after the Ottawa EPC report **and included in the original report** analyzed the performance measure outcomes in a small sample of postmenopausal women from WHI trial showed generally no differences in performance measures between vitamin D (400 IU/d) plus calcium (1000 mg/d) supplementation or placebo groups after 5 years of follow up.[258] One RCT of premenopausal women, aged 17 to 35 years old, showed that 800 IU/d of vitamin D in combination with 2000 mg/d of calcium supplementation can reduce the risk of stress fracture from military training compared to placebo.[259]

Detailed Presentation (Tables 34, 58, 59, & 60)

The current report identified two RCTs of vitamin D and calcium that assessed osteoporotic fracture risk. One, a re-analysis of data from the WHI CaD trial that attempted to assess the effects of the intervention alone (separate from use of additional personal supplements), found no significant effect of the intervention on overall fracture risk at 6 years (rated B).[2] The second RCT, the OSTPRE study, also found no effect of 3

years' supplementation with calcium and vitamin D on risk for total, nonvertebral, distal forearm, upper extremity, or lower extremity fragility fractures among 3,195 post-menopausal women, 65 to 71 years of age (rated B).[260]

One RCT on middle-age and older Australian men (age 50 to 79) tested the effect of an 18-month intervention of daily vitamin D (800IU) and calcium (1000mg) on measures of muscle function (rated A). No effect was seen on any measure of muscle function, including step test, gait speed or sway.[261]

An RCT that tested the effect of a 3-year intervention of daily vitamin D (800IU) and calcium (1000mg) on risk for falls among 812 older Finnish women (mean age 67) found no effect on fall risk (study rated C).[262]

In the original report, one RCT of female Navy recruits, aged 17 to 35 years, aimed to determine whether supplementation with vitamin D (800 IU/d) plus calcium (2000 mg/d) can reduce the risk of stress fractures from military training near the Great Lakes (41°N).[259] The median dairy intake was <1 serving/day, which provided less than 300 mg of calcium. The combined supplementation significantly reduced the risk of stress fractures by 20 percent compared to placebo. The methodological quality of this study was rated B.

One study analyzed the performance measure outcomes in a sample of 2928 postmenopausal women from the WHI trial who had objective physical function measures.[258] The results showed that physical function, measured by grip strength, chair stands, and walking time, had generally declined in postmenopausal women who were assigned to either vitamin D (400 IU/d) plus calcium (1000 mg/d) supplementation or placebo group. However, women who had received vitamin D plus calcium supplementation showed less declines in walking time than those who had received placebo. The methodological quality of this study was rated C because only a small proportion of women from the WHI trial were in the analyses and their baseline characteristics were unclear.

From the Ottawa EPC Report: Fractures—Postmenopausal Women and Older Men

Fifteen RCTs examined the effect of either vitamin D_2 or D_3 alone or in combination with calcium on total, nonvertebral and hip fractures in postmenopausal women or older men. Few trials evaluated vertebral fractures. Most trials used vitamin D_3. There were no trials identified in premenopausal women.

Meta-analysis results from 13 RCTs of vitamin D_2 or D_3 with or without calcium showed a nonsignificant reduction in the risk of total fractures that persisted when only trials of higher quality were combined. Most trials used vitamin D_3. When combining seven RCTs of vitamin D_3 (400–800 IU) plus calcium, there was a reduction in the risk of total and hip fractures. However, in a subgroup analysis (800 IU vitamin D_3), this benefit was only evident in trials of institutionalized elderly subjects. One possible explanation for the discrepancy is that the mean serum 25(OH)D concentration achieved in trials of institutionalized participants was higher than in the trials on community dwellers. The combined estimate from trials with higher end-of-study serum 25(OH)D concentrations (>74 nmol/L) was consistent with a significant reduction in the risk of fractures.

In Ottawa EPC Report: Falls—Postmenopausal Women and Older Men

Meta-analysis results from 12 RCTs demonstrated a small reduction in the risk of falls with supplemental vitamin D_2 or D_3 (oral or injectable) with or without calcium (OR 0.89, 95% CI 0.80, 0.99). The individual treatment effects ranged from OR 0.28 (95% CI 0.12, 0.67) to 1.16

(95% CI 0.70, 1.92). In the two cluster RCTs, one demonstrated a significant reduction in the risk of falls in postmenopausal women taking vitamin D_3 plus calcium (RR 0.88, 95% CI 0.79, 0.98), whereas the other trial did not show a significant reduction in the risk of falls in elderly individuals taking vitamin D_2 (RR 1.09, 95% CI 0.95, 1.25). Meta-analysis of eight RCTs of oral vitamin D_2/D_3 supplementation with calcium showed a reduction in the risk of falls, whereas four RCTs of oral vitamin D_3 alone did not. Subgroup analyses showed a significant reduction in the risk of falls when only trials of postmenopausal women were combined. Sensitivity analyses showed a significant reduction in the risk of falls when combining (1) RCTs that explicitly defined falls and the method of fall ascertainment and (2) those in which the allocation concealment was unclear. However, combining trials by degree of compliance and loss to follow up did not.

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  Not reviewed
- **19–50 y**
  The Ottawa EPC report concluded that supplementation with vitamin D (most studies used D_3) plus calcium is effective in reducing the risk of fractures in institutionalized populations, but there is inconsistent evidence that supplemental vitamin D reduces the risk of falls in postmenopausal women and older men. One RCT of female Navy recruit, aged 17 to 35 years old, showed that vitamin D (800 IU/d) in combination of calcium (2000 mg/d) supplementation can reduce the risk of stress fractures from military training compared to placebo.
- **51–70 y**
  One RCT identified for the current report found no differences in any measure of muscle strength between men (50 to 70) who received supplemental vitamin D and calcium for 18 months and those who received placebos. No new data **were identified for the original report** since the Ottawa report
- **71+**
  No new data since the Ottawa report
- **Postmenopause**
  Two studies identified for the current report (one a reanalysis of data from the WHI study) found no differences in fracture risk between women supplemented with vitamin D and calcium and placebo groups (3 to 6 years). One study analyzed the performance measure outcomes in a small sample of postmenopausal women from the WHI trial showed generally no differences in performance measures between vitamin D (400 IU/d) plus calcium (1000 mg/d) supplementation and placebo groups after 5 years of follow up.
- **Pregnant & lactating women**
  No data

Table 58. Combined vitamin D and calcium and bone health: Characteristics of RCTs published after the Ottawa EPC report (formerly Table 97) (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Lappe 2008[259] Great Lakes, IL, US (41°N) [18433305]	• Health status • Mean age (range), y • Male (%)	Assumed healthy (Navy recruits) 19 (17–35) 0	Mean dairy servings/wk = 6 (ranged 1–26)	Vit D 800 IU/d + Ca 2000 mg/d vs. Placebo	Monitor pill taking: project staff observed the galley food lines, visited recruits in their quarters, and conducted an exit interview.	
Brunner 2008[258] WHI US (various) [18755319]	• Health status • Mean age (range), y • Male (%)	nd (for the sub sample from WHI trial) 50–79 0	nd	Vit D 400 IU/d + Ca 1000 mg/d vs. Placebo	nd (however, adherence was assessed at least annually from the weight of remaining pills along with a structured interview in WHI trial)	A sub sample from WHI trial. Post hoc analyses of a RCT.
NEW Studies						
Prentice 2013[2] WHI US (various)	• Health status • Mean age (range), y • Male (%)	Post-menopausal 50–54: 14.2%; 55–59: 22.8%; 60–69: 45.5%; 70–79: 17.5%; (50–79) 0%	nd	400 IU Vit D3 + 1,000 mg elemental calcium carbonate Vs. placebo	nd	
Salovaara 2010[260] OSTPRE Study nd	• Health status • Mean age (SD), y • Male (%)	nd 67.3 (SD 1.8) 0%	Serum vitamin D: 49.1±17.7 nmol/L	400 IU cholecalciferol + 500 mg calcium carbonate Vs. control (no intervention or placebo)	nd	
Karkkainen 2010[262] OSTPRE-FPS Kuopio, Finland	• Health status • Mean age (SD), y • Male (%)	nd 67.4 (SD 1.9) Range: 65–71 0%	Intervention- 50.1 (18.8) nmol/l control- 49.2 (17.7) nmol/l (P = 0.544)	1g/daily & 800 IU/daily Vs. Placebo	78% compliance	
Kukuljan 2009[261] Victoria, Australia	• Health status • Mean age (SD), y • Male (%)	Healthy 59.9 (SD 7.4) Range: 50–79 0%	Mean dairy servings/wk = 6 (ranged 1–26)	Vit D 800 IU/d + Ca 2000 mg/d vs. Placebo	Monitor pill taking: project staff observed the galley food lines, visited recruits in their quarters, and conducted an exit interview.	

Table 59. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (stress fracture) (formerly Table 98) (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Lappe 2008[259] [18433305]	17–35 y women	Stress fracture from Navy training (ITT)	1°	2 mo	Vit D 800 IU + Ca 200 mg	139	2626	RR (Vit D+Ca)/ placebo	0.8	0.64, 0.99	0.026	B
					Placebo	170	2575					
		Stress fracture from Navy training (per protocol)	1°	2 mo	Vit D 800 IU + Ca 200 mg	126	1852	Adjusted OR (Vit D+Ca)/ placebo	0.79	0.62, 1.01	0.059	
					Placebo	160	1848					
NEW Studies												
Prentice 2013[2] WHI US (various)		Total fractures	1°	7.2 yrs	400 IU Vit D3 + 1,000 mg elemental calcium carbonate	872	7718	HR	0.97	0.88, 1.07	NR	A
					placebo	870	7584		1.00	**Reference**		
		Hip fracture			1000mg/day of Ca & 400IU/day of Vit D3	68	7718	HR	0.86	0.62, 1.20	NR	
					Placebo	80	7584		1.00	**Reference**		

Table 59. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (stress fracture) (formerly Table 98) (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Salovaara 2010[260] OSTPRE Study nd		any fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	78	1586	HR	0.83	0.61, 1.12		A
					control (no intervention or placebo)	94	1609		1.00	**Reference**		
		any nonvertebral fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	71	1586	HR	0.87	0.63, 1.19		
					control (no intervention or placebo)	82	1609		1.00	**Reference**		
		any osteoporotic fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	42	1586	HR	0.81	0.54, 1.22		
					control (no intervention or placebo)	52	1609		1.00	**Reference**		
		distal forearm fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	23	1586	HR	0.70	0.41, 1.20		
					control (no intervention or placebo)	32	1609		1.00	**Reference**		
		proximal humerus fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	6	1586	HR	1.01	0.32, 3.14		
					control (no intervention or placebo)	6	1609		1.00	**Reference**		
		hip fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	4	1586	HR	2.23	0.41, 12.29		
					control (no intervention or placebo)	2	1609		1.00	**Reference**		
		vertebral fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	9	1586	HR	0.67	0.29, 1.58		
					control (no intervention or placebo)	13	1609		1.00	**Reference**		
		upper extremity fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	41	1586	HR	0.75	0.49, 1.16		
					control (no intervention or placebo)	50	1609		1.00	**Reference**		
		lower extremity fracture	1°	3.01 yrs	400 IU cholecalciferol + 500 mg calcium carbonate	22	1586		1.02	0.58, 1.80		
					control (no intervention or placebo)	20	1609		1.00	**Reference**		

Table 59. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (stress fracture) (formerly Table 98) (updated from original report) (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Karkkainen 2010[262] OSTPRE-FPS Kuopio, Finland		Primary—No falls	1°	3 y	1g/daily & 800 IU/daily	754	1566	OR	1.05	0.91, 1.20	>0.05	C
					Placebo	740	1573	OR	1.00	**Reference**		
		Primary—Falls (≤1)			1g/daily & 800 IU/daily	1109	1566	OR	1.13	0.97, 1.32	>0.05	
					Placebo	1073	1573	OR	1.00	**Reference**		
		Primary—No fall requiring medical attention (FRMA)			1g/daily & 800 IU/daily	1308	1566	OR	0.84	0.70, 1.01	>0.05	
					Placebo	1274	1573	OR	1.00	**Reference**		
		Primary—Falls requiring medical attention (FRMA) (≤1)			1g/daily & 800 IU/daily	1488	1566	OR	0.72	0.53, 0.97	0.03	
					Placebo	1466	1573	OR	1.00	**Reference**		

Note: Outcomes cells are shaded for the Control rows.

Table 60. Combined vitamin D and calcium and bone health: Results of RCTs published after the Ottawa EPC report (performance measures) (formerly Table 99) (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change SD	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Brunner 2008[258] [18755319]	Postmenopause	Grip strength	2°	60	Vit D 400 IU + Ca carbonate 1000 mg	1185	kg	22.81	-2.49	5.81	0.15	0.24	0.52	C
					Placebo	1162		22.96	-2.64	5.69				
		Chair stands	2°	60	Vit D 400 IU + Ca carbonate 1000 mg	1065	counts	6.52	-0.38	1.81	0.04	0.08	0.603	
					Placebo	1053		6.63	-0.43	1.81				
		Walking time	2°	60	Vit D 400 IU + Ca carbonate 1000 mg	1160	seconds		0.26	6.28	-0.54	0.26	0.03	
					Placebo	1141			0.81	6.43				
NEW Studies														
Kukuljan 2009[261] Victoria, Australia	51–70 yrs	Step test	1°	18 mos	Ig & 800 IU daily	43	unit number	9.90	final= 11.4	SD=3.00	-6	-2.0, 0.75	0.38	A
					Control	42	unit number	10.30	final= 12.0	SD=3.30	reference			
		Gait speed			Ig & 800 IU daily	43	m/s	2.84	final= 2.79	SD=1.17	+0.13	-0,36, 0.62	0.60	
					Control	42	m/s	3.08	final= 2.66	SD=1.12	reference			
		Sway, eyes open, on floor			Ig & 800 IU daily	43	mm2	294.0	final=326	SD=344	+147	32.4, 261.6	0.01	
					Control	42	mm2	320.0	final=179	SD=147	reference			
		Sway, eyes closed, on floor			Ig & 800 IU daily	43	mm2	364.0	final=241	SD=192	-79	-207, 49	0.22	
					Control	42	mm2	285.0	final=320	SD=373	reference			
		Sway, eyes open, on foam			Ig & 800 IU daily	43	mm2	737.0	final=596	SD=733	+248	9, 487	0.04	
					Control	42	mm2	597.0	final=348	SD=266	reference			
		Sway, eyes closed, on foam			Ig & 800 IU daily	43	mm2	1317.00	final= 1045	SD=787	-209	-721, 303	0.42	
					Control	42	mm2	1437.00	final= 1254	SD=1489	reference			

Note: Outcomes cells are shaded for the Control rows.

Combined Vitamin D and Calcium and All-Cause Mortality

Synopsis

This synopsis is based on a meta-analysis of RCTs of combined vitamin D and calcium supplementation evaluating mortality. **No new studies were identified for this outcome**. Numerical data were extracted from previous systematic reviews. Most trials used daily regimens; in these trials, vitamin D doses ranged between 300 and 880 IU per day. Most trials combined vitamin D and calcium supplementation; when used, calcium doses ranged between 500 and 1200 mg per day.

Our meta-analysis of 11 RCTs (44,688 participants) suggests no significant relationship between combined supplementation of vitamin D and calcium all-cause mortality (RR=0.93, 95% CI 0.86, 1.01; random effects model). There is little evidence for between-study heterogeneity in these analyses. Among 8 RCTs on 44,281 postmenopausal women, the summary random effects RR was 0.93 (95% CI 0.86, 1.00), again with little evidence for between-study heterogeneity.

Although the meta-analyses suggest decreased risk for all-cause mortality with combined vitamin D and calcium supplementation, the relationship is not statistically significant in the performed analyses.

Detailed Presentation (Table 37; Figure 11)

As mentioned in the Methods section, **the original report** updated and reanalyzed published meta-analyses of mortality outcomes. **The authors of that report** drew conclusions based on **their own** analyses **and** also comment on the concordance of **these** conclusions with those of the published meta-analyses.

Relevant Published Systematic Reviews of RCTs (With Meta-Analyses)

As described in the vitamin D and all-cause mortality section, **the original report** identified two potentially eligible systematic reviews,[204,205] and selected one as the basis for our reanalysis (Autier 2007).[204] Table 37 in the "Vitamin D" section summarizes the findings of the Autier 2007 systematic review.

As detailed below, **the original report** identified one additional trial of combined vitamin D and calcium supplementation reporting all-cause mortality.[263]

Eligible Studies Published After the Systematic Reviews

The literature searches in Autier 2007 extended up to November 2006. Two additional RCT reports **were identified for the original report** published after November 2006.[131,263] One publication[131] reported on the same trial as another publication[264] in the Autier 2007 meta-analysis, and was therefore excluded from our reanalysis. The other RCT (Bjorkman 2008)[263] was included in our meta-analysis.

One three-arm RCT (Bjorkman 2008[263], n=218) compared no supplementation versus daily supplementation with 400 IU and 1200 IU of vitamin D_3 and 500 mg of calcium. Mortality was assessed at 6 months. It included people older than 65 years, with chronically impaired mobility and stable general condition. The Bjorkman 2008 RCT was assigned grade "A" for overall reporting quality.

Reanalysis

The re-analysis conducted for the original report excluded 5 of 18 trials in the Autier 2007 meta-analysis: One trial was on patients with congestive heart failure,[206] one was published only in abstract form,[207] and in the last trial the controls also received supplementation with vitamin D, albeit with a smaller dose,[208] and two used injections of vitamin D.[209,210] Altogether, 11 RCTs were included in the reanalysis of combined vitamin D and calcium supplementation and all-cause mortality (i.e., 10 out of 18 in the Autier 2007 meta-analysis, and a subsequently published one[263]).

Among the 12 trials, sample sizes ranged from 55 to 36, 282 participants, with 7 studies including more than 500 participants. Followup periods ranged from 6 to 84 months (median 24 months). Vitamin D doses in most trials ranged between 300 and 880 IU per day. One trial used 100,000 IU orally every 4 months. Calcium supplementation doses ranged between 500 to 1200 mg per day.

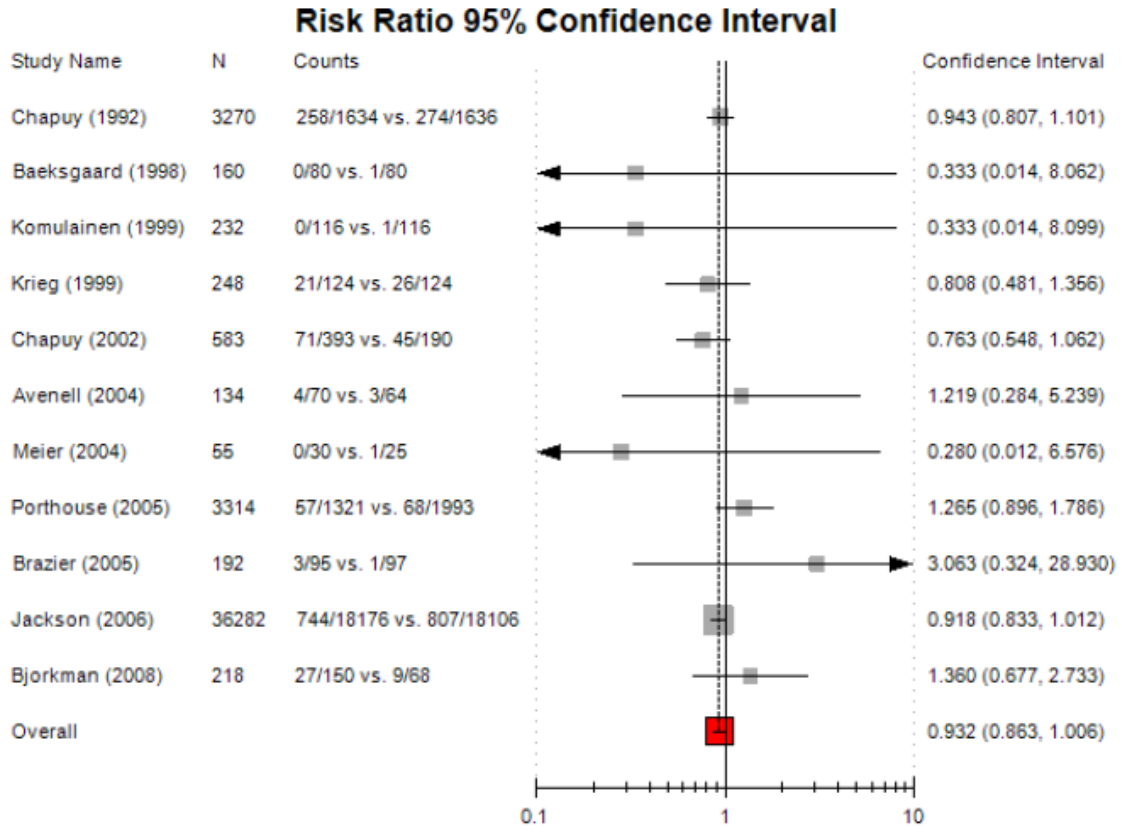
Overall, a meta-analysis of the 11 RCTs (44,688 participants; Figure 11 [formerly 22]) found no statistically significant relationship between vitamin D and all-cause mortality (RR=0.93, 95% CI 0.86, 1.01). There is little evidence for between-study heterogeneity in these analyses (P=0.58, I^2=0%). Among 8 RCTs on 44,281 postmenopausal women, the summary random effects RR was 0.93 (95% CI 0.86, 1.00), again with little evidence for between-study heterogeneity (P=0.46, I^2=0%). There are no RCTs with mean participant age below 50 years. It is unclear whether these findings are directly applicable to other life stages. In addition, in a subgroup analysis among 8 RCTs (n=8109) where the mean participant age was above 70 years, the summary random effects RR=0.98 (95% CI 0.84, 1.15), with little evidence for between study heterogeneity (P=0.33, I^2=13%).

Findings by Life Stage

- **0–6 mo**
  No data
- **7 mo–2 y**
  No data
- **3–8 y**
  No data
- **9–18 y**
  No data
- **19–50 y**
  No data
- **51–70 y**
  Our meta-analysis of 12 RCTs (44,838 participants) suggests no significant relationship between combined supplementation of vitamin D and calcium all-cause mortality (RR=0.94, 95% CI 0.87, 1.01; random effects model). There is little evidence for between-study heterogeneity in these analyses.
- **71+**
  The above are likely applicable here. In addition, in a subgroup analysis among 8 RCTs (n=8109) where the mean participant age was above 70 years, the summary random effects RR=0.98 (95% CI 0.84, 1.15), with little evidence for between study heterogeneity.

- **Postmenopause**
  Among 8 RCTs on 44,281 postmenopausal women, the summary random effects RR was 0.93 (95% CI 0.86, 1.00), again with little evidence for between-study heterogeneity.
- **Pregnant & lactating women**
  No data

Figure 11. Forest plot of trials of combined vitamin D and calcium supplementation and effects on all-cause mortality (formerly Figure 22)



Combined Vitamin D and Calcium and Hypertension and Blood Pressure

For the current report, we identified no new studies that addressed these outcomes. The original report reviewed systematic reviews and primary studies that evaluated associations between combined vitamin D and calcium intake and incidence of hypertension or change in blood pressure. For the outcome incidence of hypertension, we included RCTs and other longitudinal studies. For the outcome change in blood pressure, we included only RCTs. We included only studies of adults. Studies of pregnancy-related hypertension and blood pressure control are included in the "Pregnancy-Related Outcomes" section.

Combined Vitamin D and Calcium and Hypertension

Synopsis

No new studies were identified for this outcome. No systematic reviews that met our inclusion criteria evaluated the association between combined vitamin D and calcium intake, body stores, or serum concentrations and incidence of hypertension. The WHI trial reported an analysis of the risk of developing hypertension among the subset of women without hypertension at baseline. Over 7 years, combined vitamin D and calcium supplementation had no effect on the risk of hypertension.

Detailed Presentation (Tables 61 & 62)

The WHI trial of a combined vitamin D_3 400 IU and calcium carbonate 1000 mg supplement daily versus placebo had methodological quality B for the blood pressure outcome. The 36,282 women were postmenopausal (age 50–79 y) with a background calcium intake on average of about 1150 mg/day (from diet and supplements).[265] The women were allowed to take additional concurrent calcium and vitamin D supplements. The analysis of incident hypertension was reported briefly in a larger analysis of the blood pressure outcome (see *Combined Vitamin D and Calcium and Blood Pressure*). Among 17,122 initially nonhypertensive women, 39 percent either were prescribed medication for hypertension or developed blood pressure above 140/90 mm Hg. The adjusted HR of developing hypertension over 7 years was 1.01 (95% CI 0.96, 1.06). Among 377 women with available data, there was a statistically significant trend across subgroups based on serum 25(OH)D concentration such that combined vitamin D and calcium supplementation *increased* the risk of developing hypertension more in those women with progressively *lower* baseline 25(OH)D ($P<0.01$ for trend). Other subgroup analyses based on age, race or ethnicity, weight, or baseline total calcium intake did not find any interactions with the effect of the supplement intervention.

Findings per Intake Level

This single trial did not analyze different actual intake levels.

Findings by Age and Sex

This trial found no difference in (lack of) effect by age among postmenopausal women.

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  Not reviewed
- **19–50 y**
  No data.
- **51–70 y**
  One large trial that included women mostly within this life stage found no significant effect of combined vitamin D and calcium supplementation.
- **≥71 y**
  The WHI trial included some women within the life stage, but no study adequately evaluated this life stage.
- **Postmenopause**
  All women in the WHI trial were postmenopausal. See 51–71 y life stage.
- **Pregnant & lactating women**
  Not reviewed

Table 61. Combined vitamin D and calcium and incident hypertension: Characteristics of RCTs [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Margolis 2008[265] WHI US (various) [18824662]	• Health status • Mean age (range), y • Male (%)	No HTN 62 (50-79) 0	Ca: 1148 (654) mg/d in treatment group; 1154 (658) in placebo group 52% used Ca supplements 40% had intake ≥1200 mg/d (based on all subjects, including those with hypertension)	Combined Vit D + Ca supplement vs. Placebo	See page 242	Mean dose of open label supplemental Ca increased by <100 mg/d from 325 mg/d at enrollment; similar in both groups (based on all subjects, including those with hypertension)

Table 62. Combined vitamin D and calcium and incident hypertension: Results of RCTs [no new studies in the current report]

Author Year Study Name [PMID]	Life Stage [Subgroup]	Outcome	1°/2°	Mean Followup, y	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Margolis 2008[265] WHI [18824662]	50–79 y, Women	HTN	2°	7	Vit D_3 400 IU + Ca carbonate 1000 mg	3377	~8578	HR (Suppl/Placebo)	1.01	0.96, 1.06	0.69	B
					Placebo	3315	~8544					
	[25(OH)D <34.4 nmol/L]				Vit D + Ca	53			1.52	0.89, 2.59	NS	
					Placebo	38						
	[25(OH)D 34.4-47.6 nmol/L]				Vit D + Ca	39			1.48	0.89, 2.46	NS	
					Placebo	48						
	[25(OH)D 47.7-64.6 nmol/L]				Vit D + Ca	45			1.15	0.69, 1.92	NS	
					Placebo	45						
	[25(OH)D ≥64.7 nmol/L]				Vit D + Ca	48			0.79	0.51, 1.22	NS	
					Placebo	61						

Note: Outcomes cells are shaded for the Control rows.

Combined Vitamin D and Calcium and Blood Pressure

Synopsis

No new studies were identified that addressed this outcome. No systematic reviews that met our inclusion criteria evaluated the association between vitamin D and calcium intake, body stores, or serum concentrations, and changes in blood pressure. Two RCTs compared combined vitamin D and calcium supplementation with placebo. Both the small trial of a combined vitamin D_3 400 IU and calcium carbonate 1200 mg supplement daily and the WHI trial found no significant effect of supplementation on blood pressure after 15 weeks or 6.1 years, respectively. The WHI trial analyzed blood pressure changes in a variety of subgroups, including by age, ethnicity, baseline total calcium intake, and baseline diagnosis of hypertension, but found no significant differences in effect across any subgroup.

Detailed Presentation (Tables 63 & 64)

The WHI trial of a combined vitamin D_3 400 IU and calcium carbonate 1000 mg supplement daily versus placebo had methodological quality B for the blood pressure outcome. The 36,282 women were postmenopausal (age 50–79 y) with a background calcium intake on average of about 1150 mg/day (from diet and supplements).[265] On average, the women had normal blood pressure and were allowed to take additional concurrent calcium and vitamin D supplements. At 74 months, the women's mean systolic blood pressure had risen and diastolic blood pressure had fallen in both trial arms (by less than about 2 mm Hg each at 2 years[249]). The absolute changes were not significantly different in the women assigned to the supplement than placebo (net difference 0.2 mm Hg systolic and 0.1 mm Hg diastolic). In subgroup analyses there was no differences in results by age, ethnicity, baseline total calcium intake, baseline diagnosis of hypertension, or a variety of other factors.

The C quality trial of combined vitamin D and calcium, performed in Quebec City, recruited premenopausal women (mean age 43 y) with low calcium intake (800 mg calcium per day) who did not have severe hypertension (blood pressure over 160/95 mm Hg).[252] The mean baseline calcium intake was 704 mg/day. On average, the 63 women had normal blood pressure. They were given either combined vitamin D_3 400 IU and calcium carbonate 1200 mg daily or placebo. All women were on an energy restriction diet with a 700 kcal/day deficit. At 15 weeks, systolic and diastolic blood pressures were reduced in both study groups; systolic blood pressure was reduced by 2.5 mm Hg more in women on vitamin D and calcium than placebo, but this difference was not statistically significant. Diastolic blood pressure was reduced by the same amount in both groups. No subgroup analyses were reported. The study was limited by a 25 percent dropout rate due to lack of compliance with the diet and exercise portion of the trial, without performing an intention to treat analysis, an adequate description of the study methods, or a complete statistical analysis.

Findings per Intake Level

Both trials used similar doses, vitamin D_3 400 IU and calcium carbonate 1000 or 1200 mg daily. The background calcium intake was lower in the study of premenopausal women (800 mg/day) than the WHI trial (1150 mg/day). The WHI trial found no significant difference in (lack of) effect in subgroups with different baseline total calcium intake.

Findings by Age and Sex

Both the one small, short term, C quality trial of premenopausal women and the 6 year WHI trial of postmenopausal women found no effect. The WHI trial also found no difference in effect in subgroups of women based on age. No trials of men were found.

Findings by Life Stage

- **0–6 mo**
  Not reviewed
- **7 mo–2 y**
  Not reviewed
- **3–8 y**
  Not reviewed
- **9–18 y**
  Not reviewed
- **19–50 y**
  One small trial that included women mostly within this life stage found no significant effect of combined vitamin D and calcium supplementation.
- **51–70 y**
  One large trial that included women mostly within this life stage found no significant effect of combined vitamin D and calcium supplementation.
- **≥71 y**
  The WHI trial included some women within the life stage, but no study adequately evaluated this life stage.
- **Postmenopause**
  All women in the WHI trial were postmenopausal. See 51–71 y life stage.
- **Pregnant & lactating women**
  Not reviewed

Table 63. Combined vitamin D and calcium and blood pressure: Characteristics of RCTs (formerly Table 102) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Margolis 2008[265] WHI US (various) [18824662]	• Health status • Mean age (range), y • Male (%)	Any 62 (50-79) 0	Ca: 1148 (654) mg/d in treatment group; 1154 (658) in placebo group 52% used Ca supplements 40% had intake ≥1200 mg/d	Combined Vit D + Ca supplement vs. Placebo	See discussion of use of personal supplements in the WHI trial in "Colorectal Cancer, Detailed Presentation"	Mean dose of open label supplemental Ca increased by <100 mg/d from 325 mg/d at enrollment; similar in both groups
Major 2007[252] Quebec City, Canada (47°N) [17209177]	• Health status • Mean age (SD), y • Male (%)	Healthy, Overweight, low Ca intake 43 (5.5) 0	Ca: ~704 mg/d; all <800 mg/d	Combined Vit D + Ca supplement vs. Placebo	nd	

Table 64. Combined vitamin D and calcium and blood pressure: Results of RCTs (formerly Table 103) [no new studies in the current report]

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
SYSTOLIC BLOOD PRESSURE														
Margolis 2008[265] WHI [18824662]	50–79, Women	SBP	2°	6.1 y	Vit D_3 400 IU + Ca carbonate 1000 mg	18,176	mm Hg	127[A]	+1.1%[A]	0.9, 1.3	+0.22	-0.05, +0.49	0.11	B
					Placebo	18,106		128[A]	+0.7%[A]	0.5, 0.9				
Major 2007[252] Quebec City [17209177]	43 (5.5), Women	SBP	2°	15 wk	Vit D_3 400 IU + Ca carbonate 1200 mg (energy restriction diet)	30	mm Hg	112.4	-4.1	-6.5, -1.7	-2.5	-6.2, 1.2*	0.18	C
					Placebo (energy restriction diet)	33		109.5	-1.6	-4.2, 1.0				
DIASTOLIC BLOOD PRESSURE														
Margolis 2008[265] WHI [18824662]	50–79, Women	DBP	2°	6.1 y	Vit D_3 400 IU + Ca carbonate 1000 mg	18,176	mm Hg	76[A]	-0.2%[A]	-0.4, -0.02	+0.11	-0.04, +0.27	0.14	B
					Placebo	18,106		76[A]	-0.6%[A]	-0.8, -0.4				
Major 2007[252] Quebec City [17209177]	43 (5.5), Women	DBP	2°	15 wk	Vit D_3 400 IU + Ca carbonate 1200 mg (energy restriction diet)	30	mm Hg	74.9	-3.0	-4.8, -1.2	0	-2.7, 2.7*	1.0	C
					Placebo (energy restriction diet)	33		75.2	-3.0	-5.0, -1.0				

Note: Outcomes cells are shaded for the Control rows.
[A] Hsia 2007[249] [17309935]

Combined Vitamin D and Calcium and Bone Mineral Density or Bone Mineral Content

For the current report, we identified seven studies of the effect of combined calcium and vitamin D supplementation on bone mineral density or content (Table 66). For bone health outcomes (e.g., bone mineral density, fracture, fall or muscle strength), **the original report** relied on a recent comprehensive systematic review performed by the Ottawa EPC (**Table 34**).[8] Because the Ottawa's EPC report did not have separate analyses on the effect of vitamin D supplementation alone, the results for the effect of vitamin D alone or in combination with calcium supplementation were presented in this section.

The Ottawa EPC report was updated with literature published between January 2006 and April 2009, selected according to our eligibility criteria. For adults, only BMD indices were included. For children, only BMC indices were included. Only RCTs with duration more than 1 year qualified for inclusion.

Synopsis

Of the seven RCTs identified for this report on the effect of vitamin D and calcium supplementation on bone density or content, six reported positive effects on BMD. Followup times ranged from 1 to 6 years. Vitamin D supplementation ranged from 200 to 800IU per day, with calcium ranging from 600 to 1200mg per day.

In the original study, one RCT found that, compared to placebo, there was no significant effect of supplementation with vitamin D_3 (200 IU/d) plus calcium (1000 mg/d) on BMC changes in healthy girls, between 10 and 12 years.

Overall, findings from the Ottawa EPC report showed that vitamin D_3 (≤ 800 IU/d) plus calcium (~500 mg/d) supplementation resulted in small increases in BMD of the spine, total body, femoral neck and total hip in predominantly populations of late menopausal women.[8] Two of the three new RCTs showed consistent findings in postmenopausal women, comparing vitamin D_3 or D_2 (300 or 1000 IU/d, respectively) plus calcium (1200 mg/d) to placebo.

Detailed Presentation (Tables 34, 65, & 66)

One RCT identified for the current study that randomized 10-year-old girls in China by school compared the effects of 560mg daily calcium and 200 to 320IU vitamin D-supplemented milk per day to habitual diet and found that total body BMD was significantly increased after 2 years.[266]

A 1-year intervention with vitamin D-depleted Indian women, 16 to 36 years of age, compared the effects of 400IU vitamin D and 600mg calcium per day to those of placebo and found significantly increased femoral neck but not lumbar spine BMD (study rated A).[267]

Four studies assessed the effect of vitamin D and calcium supplementation on postmenopausal women. A study conducted on a subgroup of 1,529 WHI participants on the ability of 400IU vitamin D and 1000mg calcium per day to preserve BMD found significant effects on specific areas such as the femoral narrow neck but only trends toward increased preservation of intertrochanteric and shaft BMD at year 6 (rated A).[268] The OSTPRE-FPS trial of Finnish women, 65 to 71 years of age, found that 800IU vitamin D and 1,000 mg calcium daily significantly increased total body BMD but did not significantly increase femoral neck, lumbar spine or trochanteric BMD at 3 years (rated

C).[269] The Postmenopausal Health Study randomized 66 women, 55 to 65 years, to 300IU vitamin D and1200mg calcium or placebos daily for 12 months and then 900IU vitamin D plus 1200mg calcium for the next 18 months: Significant increases were achieved in total body and spinal BMD at 30 months (rated B).[270] The Postmenopausal Health Study II randomized 65 women, 55 to 65 years, to 400IU vitamin D and 800mg calcium or control for 12 months: Significant increases were achieved in total body but not spinal BMD (rated B).[271]

One RCT randomized 89 healthy, vitamin D-replete Australian men, 50 to 79 years of age, to milk fortified with 800IU vitamin D and 1000mg calcium per day or a control group; the fortified milk had no significant effects on BMD in any area in these men (rated A).[272]

One RCT **identified for the original report** compared the effect of vitamin D_3 (200 IU/d) plus calcium (1000 mg/d) supplementation to placebo on bone indices in healthy girls, aged 10 and 12 years.[273] The mean background dietary calcium intake was 670 mg/d. The intention-to-treat analyses showed that after 2 years of supplementation, there was no significant difference in the BMC changes between girls who received vitamin D plus calcium supplement or placebo. The methodological quality of this study was rated C, due to underpower and low compliance rate.

Three RCTs (two were rated B and one was rated C) examined the effect of vitamin D plus calcium supplementation on BMD changes. All three trials were conducted in postmenopausal women. However, the doses of vitamin D and calcium combinations varied. One RCT used daily dose of 400 IU vitamin D_3 plus 100 mg elemental calcium for 2 years.[274] The second RCT used daily dose of 1000 IU vitamin D_2 plus 1200 mg calcium citrate for 5 years.[275] The third RCT used a daily dose of vitamin D_3 300 IU plus calcium citrate 1200 mg from calcium supplemented low-fat dairy products for 1 year.[276] The latter two RCTs resulted in a significant increase in hip or total BMD comparing vitamin D plus calcium supplementation to placebo.[275,276] The one RCT that did not show significant change in femoral neck BMD comparing vitamin D plus calcium supplementation to placebo used a substantially lower dose of calcium (100 mg/d) than the other two RCTs.

In Ottawa EPC Report—Bone Mineral Density and Women of Reproductive Age, Postmenopausal Women, and Older Men

Overall, there is good evidence that vitamin D_3 plus calcium supplementation resulted in small increases in BMD of the spine, total body, femoral neck and total hip. Based on included trials, it was less certain whether vitamin D_3 supplementation alone has a significant effect on BMD.

Seventeen RCTs evaluated the effect of supplemental vitamin D_2 or D_3 on BMD, predominantly in populations of late menopausal women. Only one small RCT included premenopausal women, and two trials included older men (> 60 years). Most trials were two to three years in duration and used vitamin D doses of ≤ 800 IU daily. Most trials used vitamin D_3 and also included calcium 500 mg as a cointervention.

Meta-analysis results of 17 RCTs of vitamin D_3 plus calcium versus placebo were consistent with a small effect on lumbar spine, femoral neck, and total body BMD. The WHI trial found a significant benefit of 400 IU vitamin D_3 plus 1000 mg calcium supplementation on total hip BMD. However, when the effect of vitamin D_3 plus calcium versus calcium alone supplementation is assessed, no significant increase in BMD was observed with either

intervention, suggesting vitamin D_3 may be of less benefit in calcium replete postmenopausal women. Vitamin D_3 alone versus placebo did not result in a significant increase in BMD in postmenopausal women, except in one trial that noted an increase in femoral neck BMD. Only a few trials reported the impact of baseline serum 25(OH)D concentrations on BMD and in all of these trials, baseline 25(OH)D concentration was not associated with increased BMD.

Findings by Life Stage

- **0–6 mo**
  No data
- **7 mo–2 y**
  No data
- **3–8 y**
  No data
- **9–18 y**
  One RCT showed that, compared to placebo, there was no significant effect of vitamin D_3 (200 IU/d) plus calcium (1000 mg/d) on BMC changes in healthy girls, aged between 10 and 12 years old.
- **19–50 y**
  No data
- **51–70 y**
  No new data since the Ottawa EPC report
- **≥71 y**
  No new data since the Ottawa EPC report
- **Postmenopause**
  Findings from the Ottawa EPC report showed that vitamin D_3 (≤ 800 IU/d) plus calcium (~500 mg/d) supplementation resulted in small increases in BMD of the spine, total body, femoral neck, and total hip in predominantly populations of late menopausal women. Two of the three new RCTs showed a significant increase in hip or total BMD in postmenopausal women, comparing D_3 or D_2 (300 or 1000 IU/d, respectively) plus calcium (1200 mg/d) to placebo.
- **Pregnant & lactating women**
  No new data since the Ottawa EPC report

Table 65. Combined vitamin D and calcium and bone mineral density/content: Characteristics of RCTs published after the Ottawa EPC report (formerly Table 104) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Cheng 2005[273] Jyvaskyla, Finland (62°24'N) [16280447]	• Health status • Mean age (range), y • Male (%)	Healthy 11.2 (10–12) 0	Diet Vit D: 100 IU/d Ca: 670 mg/d	Vit D_3 200 IU/d + Ca carbonate 1000 mg/d vs. placebo	65% completed intervention with >50% compliance	
Bolton-Smith 2007[274] (UK 54ºN) [17243866]	• Health status • Mean age (range), y • Male (%)	Healthy (assumed postmenopausal) 68 (≥60) 0	25(OH)D: 59.4 nmol/L Ca: 1548 mg/d	Vit D_3 400 IU/d + Elemental Ca 100 mg/d vs. placebo	Good supplement adherence based on pill count (median, 99; IQE 97.3–99.8%).	Noncompliant women were excluded.
Zhu 2008[275] CIFOS Western Australia [18089701]	• Health status • Mean age (SD), y • Male (%)	nd (assumed postmenopausal) 74.8 (2.6) 0	25(OH)D: 68.0 nmol/L Ca: 1010 mg/d	Vit D_2 1000 IU/d + Ca citrate 1200 mg/d vs. placebo	No differences in adherence among groups (81–89% by tablet counting)	
Moschonis 2006[276] Greece (31ºN) [17181890]	• Health status • Mean age (range), y • Male (%)	Postmenopausal 61 (55–65) 0	Diet Vit D: 23.6 IU/d Ca 680 mg/d	Vit D_3 300 IU/d + Ca 1200 mg/d (from low fat dairy products) vs. control (usual diet)	Dairy group 93% (assessed via information obtained at the biweekly sessions	Control group had no intervention (or usual diet) so compliance issue not applicable
NEW Studies						
Islam 2010[267] Dhaka, Bangladesh	• Health status • Mean age (range), y • Male (%)	Healthy 22.9 (SD 3.9) 0%	placebo-35.0 +/- 9.4 nmol/L Vit D-37.1+/- 12.1 nmol/L VitD+Ca-37.8+/-10.9 nmol/L MMN+D+Ca-36.9+/-12.5 nmol/L	VD (Vit D 10 µg)/day Vs. VD-Ca (Vit D 10 µg + calcium 600 mg)/day Vs. Placebo	compliance not given but 18.5% dropped out	

Table 65. Combined vitamin D and calcium and bone mineral density/content: Characteristics of RCTs published after the Ottawa EPC report (formerly Table 104) [no new studies in the current report] (continued)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Jackson 2011[268] WHI US (various)	• Health status • Mean age (range), y • Male (%)	Post menopausal nd 0%	vitamin D intake: placebo- 7.54+/-6.36 ug/d, CaD-7.42+/-5.84 ug/d calcium intake: placebo- 1049+/-625.7 mg/d, CaD-1,039+/-635.1 mg/d	(400 IU Vit D_3+1000 mg elemental calcium)/day Vs. placebo	80% or greater compliance-968 women (placebo = 500, CaD= 468)	
Karkkainen 2010[269] OSTPRE-FPS Kuopio, Finland	• Health status • Mean age (SD), y • Male (%)	Post menopausal 67.4 (SD 1.9) 0%	intervention- 50.1 (18.8) nmol/l control- 49.2 (17.7) nmol/l (p=0.544)	Vit D 800 IU+calcium 1,000 mg Vs. control (neither supplementation nor placebo)	79% compliance	
Kukuljan 2011[272] Geelong, Australia	• Health status • Mean age (range), y • Male (%)	Healthy 59.9 (SD 7.4) 100%	calcium intake: 911–1064 mg/d Serum vitamin D level: 86.3+/-36.0 nmol/L	fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D_3) vs. controls	exercise program- 63% (95% CI: 57, 69) fortified milk- 90% (95% CI, 87, 93),	
Moschonis 2011[271] Postmenopausal Health Study Greece	• Health status • Mean age (range), y • Male (%)	Healthy 62.4 (SD 5.3) 0%	Vitamin D intake: 0.89±0.66ug/d Calcium intake: 789.6±213.5mg/d	CaD (800 mg calcium+10 µg Vit D_3)/day Vs. control	NR	
Moschonis 2010[270] Postmenopausal Health Study Greece	• Health status • Mean age (SD), y • Male (%)	Healthy 60.7 (SD 5) 0%	Vitamin D intake: 0.61±0.61 ug/d Serum vitamin D level:26.2±8.5 nmol/L Calcium intake: 682.9±226.1 mg/d	(1200 mg calcium+7.5 µg D_3)/day for the first 12 months + (1200 mg calcium+22.5 µg D_3)/day for the next 18 months Vs. control (neither counselling nor dietary products)	nd	
Zhu 2008[266] Beijing, China	• Health status • Mean age (range), y • Male (%)	Healthy 10.1 (SD 0.3) 0%	Vit D intake Control group—0.9 ± 0.6µg/d CaD milk—0.9 ± 0.6µg/d	560 mg calcium + 5-8 µg Vit D/school day Vs. control (no supplementary milk and habitual diet)	nd	

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report]

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Cheng 2005[273] [16280447]	10–12 y girls	BMC	1°	24	Vit D 200 IU + Ca carbonate 1000 mg	46	kg	1.3	34.70%	34.3%, 35.1 %	-0.3%	-0.8, 0.2[A]	NS	C
					Placebo	39		1.3	35.00%	34.6%, 35.4 %				
Bolton-Smith 2007[274] [17243866]	Postmeno-pausal women	Femoral neck BMD	nd	24	Vit D_3 400 IU + Elemental Ca 100 mg	50	mg/cm^2	nd	1.9	-6.5, 10.3	1.2	-12.6, 15.0[A]	NS	B
					Placebo	56		nd	0.7	-10.2, 11.6				
Zhu 2008[275] Australia CIFOS [18089701]	Postmeno-pausal women	Hip BMD	1°	60	Vit D_2 1000 IU + Ca citrate 1200 mg	39/33[B]	mg/cm^2	783	nd		2.20%	1.9, 2.5	0.05	B
					Placebo	41/36[B]		828	nd					
Moschonis 2006[276] [17181890]	Postmeno-pausal women	Total body BMD	1°	12	Vit D_3 300 IU + Ca 1200 mg (from low fat dairy products)	39	mg/cm^2	1.13	1.50%	0.9%, 2.2%	2.20%	1.3, 3.1[A]	<0.05	C
					Control (usual diet)	36		1.12	-0.70%	-1.4%, -0.1%				
NEW Studies														
Islam 2010[267]	9–18, 19–50 yrs	Femoral neck BMC	1°	1 yr	VD (Vit D 10 µg)/day	40	g	3.384	change=0.061	sd=0.205	+0.14	0.05, 0.22	<0.001	A
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g	3.436	change=0.069	sd=0.174	+0.14	0.07, 0.22	<0.001	
					Placebo	35	g	3.316	change=-0.075	sd=0.146				
		Femoral neck BMD			VD (Vit D 10 µg)/day	40	g/cm^2	0.8	change=0.012	sd=0.028	+0.02	0.01, 0.03	<0.001	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm^2	0.799	change=0.013	sd=0.030	+0.02	0.01, 0.03	<0.001	
					Placebo	35	g/cm^2	0.768	change=-0.010	sd=0.012				

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report] (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
		Lumbar spine L2-L4 BMC			VD (Vit D 10 µg)/day	40	g	32.548	change=0.620	sd=2.442	+0.58	-0.84, 2.00	0.42	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g	31.782	change=0.687	sd=2.761	+0.65	-0.82, 2.12	0.39	
					Placebo	35	g	32.399	change=0.042	sd=3.673				
		Lumbar spine L2-L4 BMD			VD (Vit D 10 µg)/day	40	g/cm^2	0.898	change=0.013	sd=0.036	+0.02	-0, 0.04	0.12	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm^2	0.895	change=0.010	sd=0.042	+0.01	-0.01, 0.03	0.22	
					Placebo	35	g/cm^2	0.891	change=-0.003	sd=0.049				
		Trochanter BMC			VD (Vit D 10 µg)/day	40	g	5.818	change=0.158	sd=0.549	+0.31	0.09, 0.53	0.01	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g	5.877	change=0.090	sd=0.419	+0.24	0.06, 0.43	0.01	
					Placebo	35	g	5.885	change=-0.151	sd=0.389				
		Trochanter BMD			VD (Vit D 10 µg)/day	40	g/cm^2	0.634	change=0.002	sd=0.021	+0.02	0.01, 0.03	0.002	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm^2	0.625	change=0.001	sd=0.026	+0.02	0.01, 0.03	0.01	
					Placebo	35	g/cm^2	0.619	change=-0.017	sd=0.029				
		Ward's triangle BMD			VD (Vit D 10 µg)/day	40	g/cm^2	0.654	change=0.010	sd=0.035	+0.03	0.01, 0.04	<0.001	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm^2	0.654	change=0.015	sd=0.031	+0.03	0.02, 0.05	<0.001	
					Placebo	35	g/cm^2	0.628	change=-0.018	sd=0.027				

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report] (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Jackson 2011[268]	Postmeno-pause	Intertrochanteric BMD	1°	year 6	(400 IU Vit D_3+1000 mg elemental calcium)/day	777	g/cm^2	0.746	final=0.749	sd=0.135	+0.02	0.01, 0.04	<0.001	A
					placebo	751		0.725	final=0.725	sd=0.137				
		Narrow neck BMD			(400 IU Vit D_3 + 1000 mg elemental calcium)/day	777		0.736	final=0.742	sd=0.133	+0.02	0.01, 0.03	0.003	
					placebo	751		0.723	final=0.722	sd=0.136				
		Shaft BMD			(400 IU Vit D_3 + 1000 mg elemental calcium)/day	777		1.18	final=1.199	sd=0.189	+0.03	0.01, 0.05	<0.001	
					placebo	751		1.155	final=1.165	sd=0.190				
Karkkainen 2010[269] OSTPRE-FPS	51–70 yrs	Femoral neck BMD	1°	3 yrs	Vit D 800 IU + calcium 1,000 mg	280	g/cm^2	0.866	final=0.848	sd=0.13	-0.002	-0.02, 0.02	0.85	C
					control (neither supplementation nor placebo)	311		0.865	final=0.850	sd=0.12				
		Lumbar spine BMD			Vit D 800 IU + calcium 1,000 mg	259		1.039	final=1.047	sd=0.17	0.013	-0.04, 0.02	0.37	
					control (neither supplementation nor placebo)	285		1.052	final=1.060	sd=0.17				
		Total body BMD			Vit D 800 IU+calcium 1,000 mg	195		1.069	final=1.078	sd=0.10	-0.003	-0.02, 0.02	0.76	
					control (neither supplementation nor placebo)	238		1.079	final=1.081	sd=0.10				
		Total proximal femur BMD			Vit D 800 IU+calcium 1,000 mg	280		0.948	final=0.934	sd=0.14	-0.005	-0.03, 0.02	0.65	

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report] (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
					control (neither supplementation nor placebo)	310		0.953	final=0.939	sd=0.13				
		Trochanter BMD			Vit D 800 IU+calcium 1,000 mg	280		0.783	final=0.779	sd=0.13	-0.01	-0.03, 0.01	0.31	
					control (neither supplementation nor placebo)	310		0.797	final=0.790	sd=0.13				
		Ward's triangle			Vit D 800 IU + calcium 1,000 mg	280		0.67	final=0.652	sd=0.14	-0.001	-0.02, 0.02	0.93	
					control (neither supplementation nor placebo)	310		0.672	final=0.653	sd=0.13				
Kukuljan 2011[272]		L1-L3 total volumetric BMD	1°	18 months	fortified milk (400 ml/day containing 1000 mg calcium + 800 IU Vit D_3)	45	g/cm^3	164	change=-0.6	-2.1, 0.8	-0.6	-2.7, 1.6	0.61	
	51–70, 71+ yrs				controls	44		171	change=-0.05	-1.5, 1.4				A
		L1-L3 trabecular volumetric BMD			fortified milk (400 ml/day containing 1000 mg calcium + 800 IU Vit D_3)	45		115	change=-1.5	-3.1, 0.9	-2.3	-6.4, 1.8	0.26	
					controls	44		120	change=0.8	-2.9, 1.2				
		mid-femur cortical volumetric BMD			fortified milk (400 ml/day containing 1000 mg calcium + 800 IU Vit D_3)	45		1104	change=-1.0	-1.4, -0.6	-0.3	-1.0, 0.4	0.41	
					controls	44		1108	change=-0.7	-1.3, -0.2				
		mid-tibia cortical volumetric BMD			fortified milk (400 ml/day containing 1000 mg calcium + 800 IU Vit D_3)	45		1105	change=-1.2	-1.7, -0.7	-0.1	-0.8, 0.6	0.78	
					controls	44		1113	change=-1.1	-1.6, -0.5				

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report] (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Moschonis 2011[271] Postmeno-pausal Health Study	Postmeno-pause	heel BMD	1°	12 months	CaD (800 mg calcium + 10 µg Vit D_3)/day	26	g/cm^2	0.476	final=0.459	sd=0.081	-0.002	-0.04, 0.04	0.92	B
					Control	39		0.472	final=0.461	sd=0.083				
		L2-L4 BMD			CaD (800 mg calcium + 10 µg Vit D_3)/day	26		1.121	final=1.113	sd=0.160	+0.01	-0.07, 0.10	0.77	
					control	39		1.134	final=1.101	sd=0.167				
		total body BMD			CaD (800 mg calcium+10 µg Vit D_3)/day	26		1.112	final=1.135	sd=0.083	+0.04	0, 0.08	0.05	
					control	39		1.095	final=1.094	sd=0.079				
Moschonis 2010[270] Postmeno-pausal Health Study		pelvis BMD	1°	30 months	(1200 mg calcium+7.5 µg D_3)/day for the first 12 months + (1200 mg calcium+22.5 µg D_3)/day for the next 18 months	35	g/cm^2	1.096	final=1.089	sd=0.087	+0.02	-0.02, 0.06	0.30	B
					control (neither counselling nor dietary products)	31		1.067	final=1.067	sd=0.084				
		total body BMD			(1200 mg calcium+7.5 µg D_3)/day for the first 12 months + (1200 mg calcium+22.5 µg D_3)/day for the next 18 months	35		1.134	final=1.135	sd=0.067	+0.03	-0.01, 0.06	0.11	
					control (neither counselling nor dietary products)	31		1.124	final=1.106	sd=0.078				

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report] (continued)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
		total spine BMD			(1200 mg calcium+7.5 µg D_3)/day for the first 12 months + (1200 mg calcium+22.5 µg D_3)/day for the next 18 months	35		1.119	final=1.234	sd=0.135	+0.04	-0.03, 0.11	0.23	
					control (neither counselling nor dietary products)	31		1.139	final=1.193	sd=0.139				
Zhu 2008[266]	9–18 yrs	midriff BMDsc	1°	2 yrs	560 mg calcium + 5–8 µg Vit D/school day	112	mg/cm$^{1.586}$	1585	final=1803	sd=446	+43	-79, 165	0.49	B
					control (no supplementary milk and habitual diet)	123	mg/cm$^{1.586}$	1584	final=1760	sd=499				
		pelvis BMDsc			560 mg calcium + 5–8 µg Vit D/school day	112	mg/cm$^{3.082}$	46	final=49	sd=7	0	-1.9, 1.9	1	
					control (no supplementary milk and habitual diet)	123	mg/cm$^{3.082}$	47	final=49	sd=8				
		total body BMDsc			560 mg calcium + 5–8 µg Vit D/school day	112	mg/cm$^{2.528}$	93	final=95	sd=10	+3	0.3, 5.7	0.03	
					control (no supplementary milk and habitual diet)	123	mg/cm$^{2.528}$	95	final=92	sd=11				

Note: Outcomes cells are shaded for the Control rows.
[A] Estimated from reported data.
[B] Baseline/followup number of subjects analyzed.

How Does Dietary Intake of Vitamin D From Fortified Foods and Vitamin D Supplementation Affect Serum 25(OH)D Concentrations (Arrow 4)?

The evidence for this question comes from studies identified in our literature search that crossed vitamin D terms with various outcomes terms **as well as a high-quality systematic review**. Studies that addressed this question but do not report any of the outcomes of interest would not have been identified in this manner. Because the availability of serum 25(OH)D concentration is unlikely to be adequately indexed in the MEDLINE® citation, it would be difficult to comprehensively search the literature for this question. To do so would require retrieving all vitamin D supplements full text articles (in excess of 10,000) to look for serum 25(OH)D concentration data. Given that there is no plausible reason for a systematic bias of studies of a specific outcome choosing to report serum 25(OH)D concentration, we believe that the evidence found, while not comprehensive, is a small but representative random sample. Only RCTs were included for this question. RCTs of different regimens but with the same dose of vitamin D supplementation were excluded (e.g., comparison of daily, weekly versus monthly dose).

This question was also addressed in the Ottawa EPC report.[8] When appropriate, we extracted relevant data from the Ottawa EPC report to be incorporated into our analyses.

RCTs on Dietary Intakes of Vitamin D From Fortified Foods and Serum 25(OH)D Concentrations

Synopsis

The current report identified one systematic review published since the original report that addressed the question as well as eighteen new RCTs that met the inclusion criteria (two that used fortified foods and the remainder that used supplements). The systematic review reported widely varying increases in serum concentrations of 25(OH) for similar doses of vitamin D, with a general increase in serum concentration with dietary intake.

For the original report, the updated search did not identify new RCT evaluating the effect of food fortification on serum 25(OH)D concentrations since the Ottawa EPC report.[8] The Ottawa EPC report concluded that there is "good" evidence that dietary intake of vitamin D increases serum 25(OH)D concentrations among adults.

Detailed Presentation

The current report identified one quality systematic review that addressed the relationship between vitamin D supplementation and net change in serum 25(OH)D concentrations.[277] This review included 76 placebo-controlled and open-label trials published from 1984 through 2011 that assessed the effects of vitamin D supplementation (most trials used oral doses, although a small number of studies administered vitamin D via injection). Doses tested ranged from 200 to 10,000IU per day. Similar doses resulted in increases in serum 25(OH)D that varied by three to

four fold. Meta-regression showed that serum concentrations increased by an average of 1.95 nmol/L for each 40IU per day supplementation; use of ergocalciferol in place of cholecalciferol resulted in smaller increases, and simultaneous supplementation with calcium resulted in non-significantly smaller increases in serum 25(OH)D concentrations. The small number of trials that used higher doses precludes assessment of whether the dose-response relationship plateaus at higher doses. Most studies did not stratify findings by sex, and the review itself did not stratify findings by assay method.

Eighteen of the RCTs that met inclusion criteria for the current report could be included in an assessment of dose response (Table 67). Two of the studies provided the Vitamin D as fortified foods;[229,272] the remainder administered supplemental vitamin D alone or in combination with calcium.[150,186,188,228,230,231,234-236,244,245,248,260,267,269,278] One study administered ergocalciferol.[188]

All studies reported an increase in serum 25(OH)D with supplementation. However, the studies varied by age group and health status of participants, baseline vitamin D status, dose, duration, and assay used to assess serum 25(OH)D. Further information on assay methods and performance is provided in Appendix G.

RCTs on Vitamin D Supplementation and Serum 25(OH)D Concentrations

Synopsis

Because the availability of serum 25(OH)D concentration is unlikely to be adequately indexed in the Medline citation, it would be difficult to comprehensively search the literature for this question. We believe that studies summarized here are a small but representative random sample of all available data.

We plotted the net changes in serum 25(OH)D concentration against the doses of vitamin D supplementation using data from 44 RCTs with 50 comparisons in adults and children. Only RCTs of daily vitamin D_3 supplementation (doses ranged from 200 to 5000 IU/d) alone or in combination with calcium supplementation (doses ranged from 500 to 1550 mg/d) that provided sufficient data for the calculations were included in the plot. It is important to note that the studies had varied compliance rates in the vitamin D intake; limited or no adjustment for skin pigmentations, calcium intake, or background sun exposure; different vitamin D assay methodologies and measurement (both intra- and interassay) variability. All these factors increase the heterogeneity and limit the usefulness of an overall summary estimate for an intake dose response in serum 25(OH)D concentration. Nonetheless, the relationship between increasing doses of vitamin D_3 with increasing net change in 25(OH)D concentration was evident in both adults and children (Figure **12**). It was also apparent that the dose-response relationships differ depending on study participants' serum 25(OH)D status (≤40 vs. >40 nmol/L) at baseline (Figure **13**), and depending on duration of supplementation (≤3 vs. >3 months) (Figure **14**). **For the current report, we also plotted the relationship between dose of vitamin D_3 and net change in 25(OH)D concentration according to the assay method reported (Figure 15).** Vitamin D_2 supplementation was more commonly used in RCTs of infants and pregnant or lactating women, than vitamin D_3 supplementation. Results showed that

supplementation of vitamin D_2 significantly increased 25(OH)D concentrations in infants, lactating mothers and in cord blood.

Detailed Presentation (Table 67; Figures 12, 13, 14, & 15)

The results from 26 RCTs with 28 comparisons in adults and two RCTs with three comparisons in children evaluating the effect of vitamin D_3 supplementation alone or in combination with calcium supplementation on serum 25(OH)D concentrations are shown in Table 67. Most of the data **included in the original report** were extracted directly from the Ottawa EPC report. In adults **included in studies from both the original and the current report**, the doses of vitamin D_3 ranged from 200 to 5000 IU/d, and the doses of calcium supplementation ranged from 500 to 1550 mg/d across the comparisons. In children, the doses of vitamin D_3 ranged from 200 to 2000 IU/d. Duration of supplementation ranged from 0.5 to 60 months. Study populations and baseline vitamin D concentrations varied across these comparisons.

Figure 15 shows the dose-response results by reported assay method. Most studies reported using a radioimmunoassay, a radioreceptor assay (a heterogeneous group, as a number of different molecules are used as receptors), or a method involving HPCL-tandem mass spectrometry; few studies reported using a chemiluminescence assay (CLIA) or enzyme linked immunoadsorption assay (ELISA). The plots show slightly different patterns for the different assays.

The remainder of this section reports the results of the dose response assessment conducted for the 2006 evidence review and described in the original report.

Ottawa EPC Report -Adults

There were eleven RCTs (n=1281) of which seven (n=668) permitted a quantitative analysis. Ten of eleven trials found a significant effect of dietary intake from foods fortified with vitamin D on serum 25(OH)D concentrations. There was significant heterogeneity of the treatment effect. Potential sources of heterogeneity are the different 25(OH)D assays used (two studies each used HPLC, RIA or CPBA, and one study did not report the assay), the dietary vehicles used, and study populations. The increase in serum vitamin D concentration in the seven trials ranged from 15 (95% CI 11, 18) to 40 (95% CI 25, 55) nmol/L (fortification consisting of 100–1000 IU of vitamin D).

There can be a potential confounding of the data by the food source, the assay used to measure 25(OH)D and potential differences in the bioavailability and/or metabolism of vitamin D_2 versus vitamin D_3. Most studies in this review used dairy products as the source of fortified food. It is important to note that there is potential for study contamination through altered intake of other nutrients such as calcium, phosphate and acid load that can affect the study outcomes.

Ottawa EPC Report—Infants

Seven RCTs included infants and few trials used vitamin D_3 supplementation. One RCT concluded that 200 IU of vitamin D_2 may not be enough to prevent vitamin D deficiency in those infants residing at northern latitudes. A dose-response relationship was noted in this trial (100, 200, 400 IU/day). Consistent responses to vitamin D supplementation were noted across the seven trials, and some trials suggested that infants

who are vitamin D deficient may respond differently and require higher doses of vitamin D to achieve serum 25(OH)D concentrations within the normal range.

Ottawa EPC Report—Pregnant or Lactating Women

There were six small RCTs of vitamin D supplementation in pregnant or lactating women. No randomized trials studied the effect of 400 IU vitamin D_3/d. Three trials used 1000 IU vitamin D_2/d and one trial used 1000 IU/d of vitamin D_3. Supplementation of vitamin D_2 1000–3600 IU/d and vitamin D_3 1000 IU/d resulted in significant increases in serum 25(OH)D concentrations in lactating mothers and in cord blood. One trial found that supplementation of lactating mothers with 1000 IU vitamin D_2/d during winter months did not significantly increase serum 25(OH)D concentrations in the infants.

Ottawa EPC Report—Children and Adolescents

There were four trials that examined the effect of vitamin D on serum 25(OH)D concentrations in children or adolescents with doses ranging from 200 to 2000 IU of vitamin D_3 per day and 400 IU of vitamin D_2. There were consistent increases in serum 25(OH)D concentrations ranging from 8 nmol/L (200 IU/d), 16.5 (with 600 IU D_3/d) to 60 nmol/L (2000 IU of vitamin D_3/d).

Ottawa EPC Report—Premenopausal Women and Younger Men

Ten small trials included premenopausal women and younger males. Three trials compared vitamin D_2 to vitamin D_3 in healthy young adults. Two of the three trials used RIA, and one used HPLC to measure serum 25(OH)D concentrations The doses of vitamin D_3 ranged from 600 to 10,000 IU/day and vitamin D_2 (4000 IU/d or 50,000 to 100,000 for single dose).

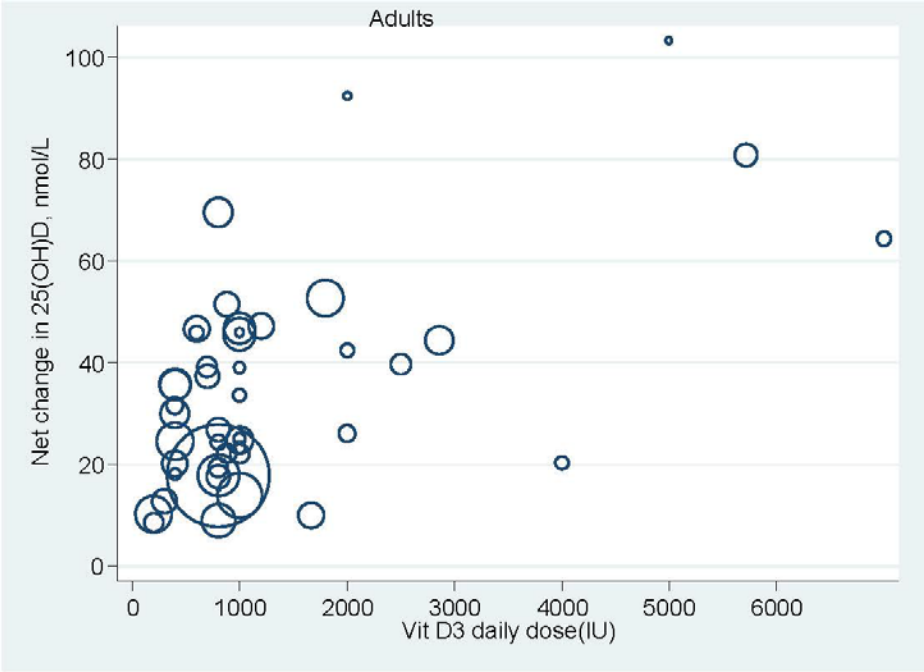
Three trials found that supplementation with vitamin D_2 and D_3 in healthy adults may have different effects on serum 25(OH)D concentrations. One trial compared 100,000 IU vitamin D_2 given orally versus injection and found a greater variability in response with the intramuscular preparation. There appeared to be dose-response effect in those trials that used multiple doses of vitamin D_3, although there were insufficient data to perform a meta-analysis.

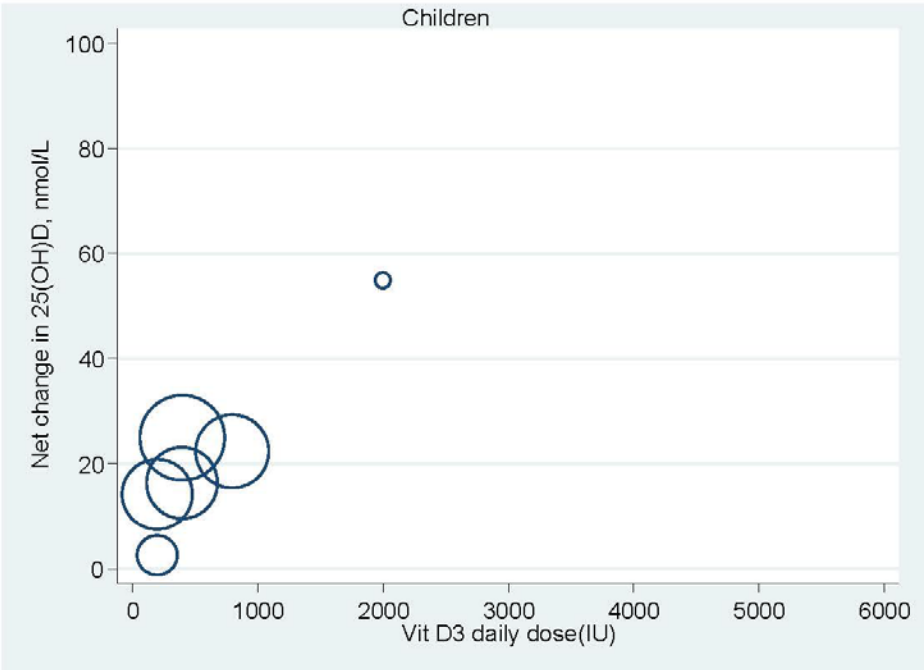
Ottawa EPC Report—Postmenopausal Women and Older Men

Forty-four trials were conducted exclusively in postmenopausal women and older men, with 14 of these in elderly populations living in long-term care or nursing homes. One trial enrolled only women in early menopause (n=129). Doses of vitamin D_3 ranged from 100 to 4000 IU/day and vitamin D_2 was 9000 IU/day. One trial was conducted in African American women.

One trial found that wintertime declines in serum 25(OH)D concentrations were prevented with 500 IU vitamin D_3 per day. A dose response with increasing doses of vitamin D_3 was noted for serum 25(OH)D concentrations. There was variability in response to similar doses across trials that may have been due to differences in serum 25(OH)D assays or baseline 25(OH)D concentrations. Similarly, although some trials reported a greater response to vitamin D in populations that were vitamin D deficient at baseline compared to those who were not, there were insufficient data on which to base a definitive conclusion on this point.

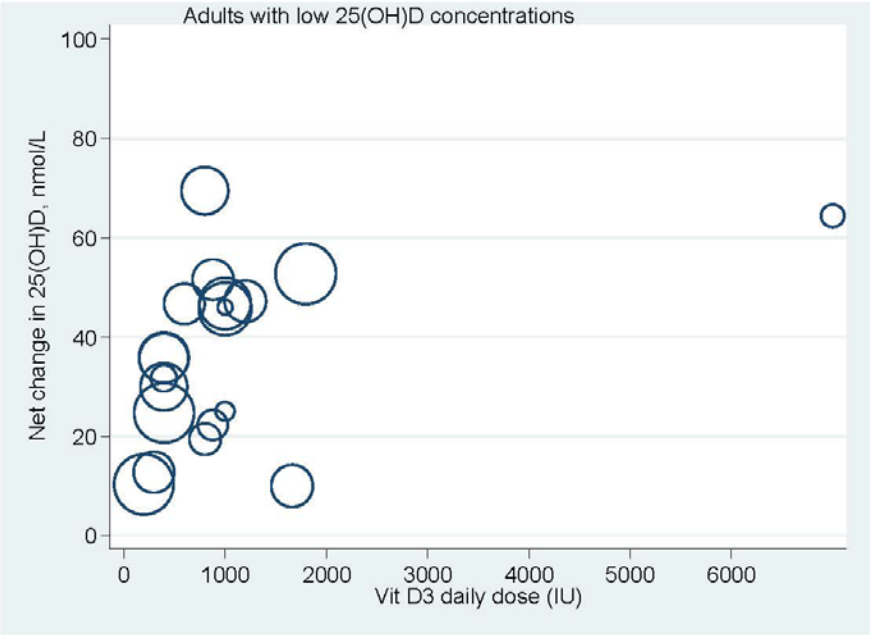
Figure 12. Relationship between doses of vitamin D_3 supplementation and net changes in serum 25(OH)D concentrations in RCTs (formerly Figure 23)

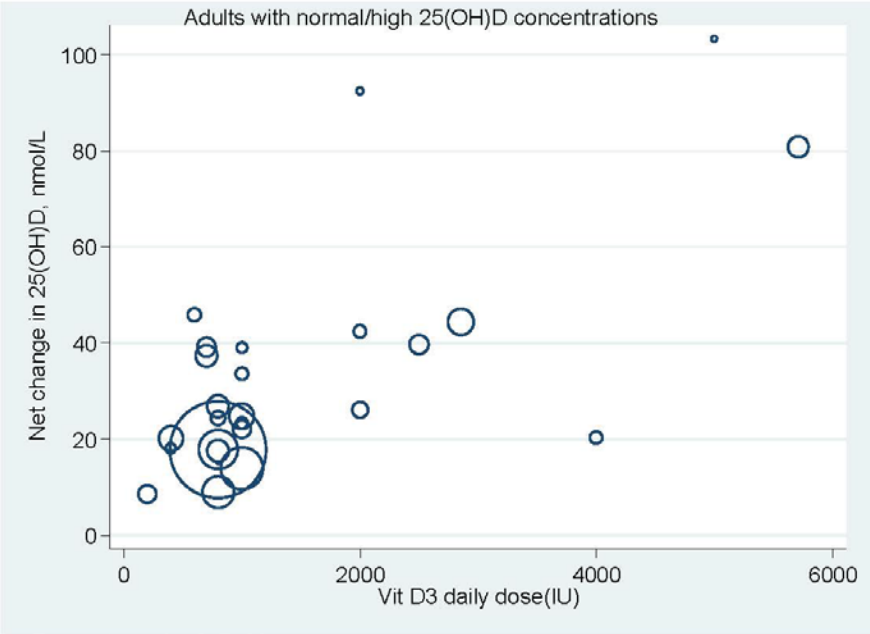




Legends: Each empty circle represents one study. The area of the circle is proportional to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D.

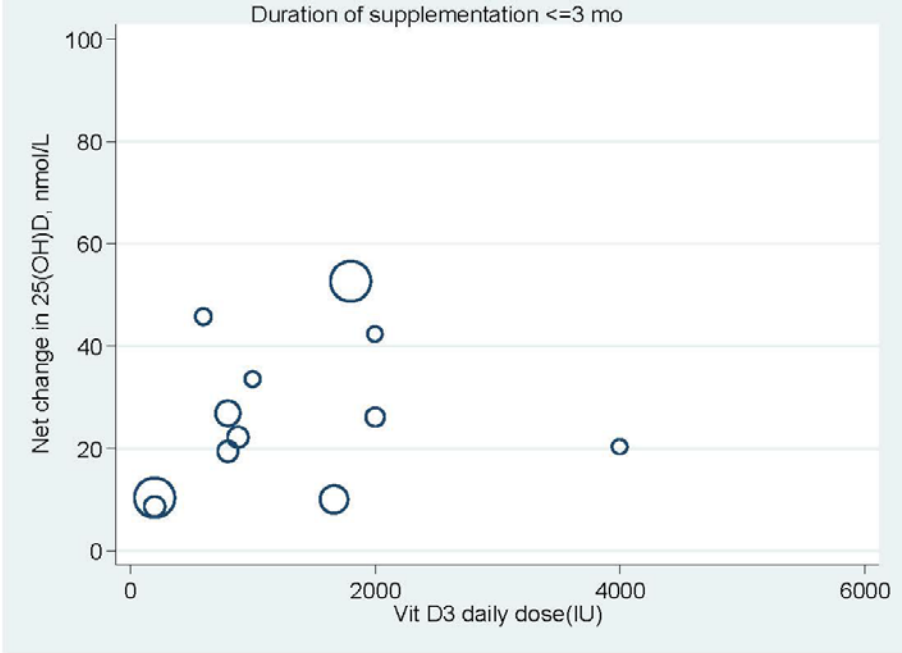
Figure 13. Relationship between doses of vitamin D_3 supplementation and net changes in serum 25(OH)D concentrations in RCTs by baseline vitamin D status among adults (formerly Figure 24)

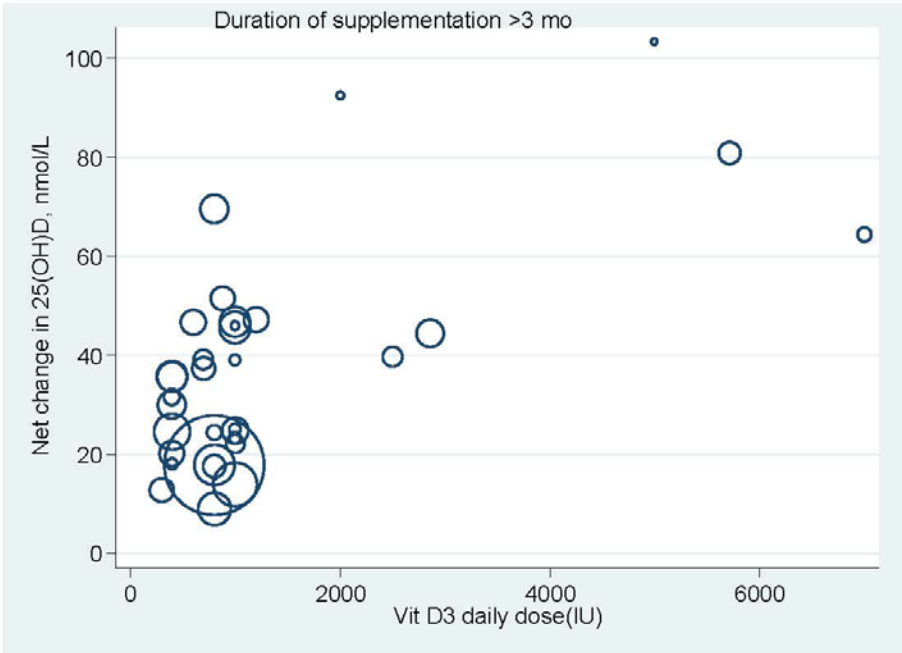




Legends: Each empty circle represents one study. The area of the circle is proportional to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D.

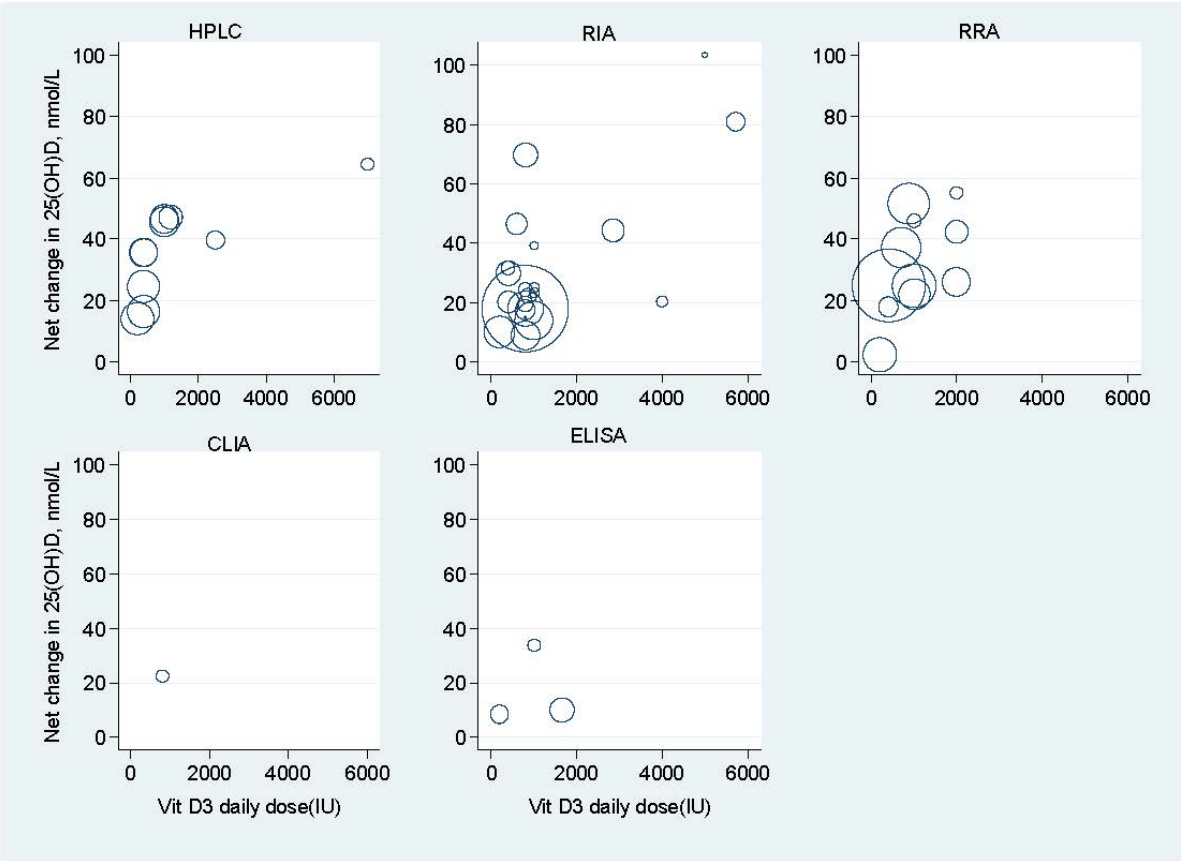
Figure 14. Relationship between doses of vitamin D_3 supplementation and net changes in serum 25(OH)D concentrations in RCTs by duration of supplementation among adults (formerly Figure 25)





Legends: Each empty circle represents one study. The area of the circle is proportional to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D.

Figure 15. Relationship between doses of vitamin D_3 supplementation and net changes in serum 25(OH)D concentrations in RCTs by assay type (new figure)



Legends: Each empty circle represents one study. The area of the circle is proportional to the inverse of the within-study variances. Typically, the larger the bubble, the larger the sample size and the smaller the standard error of the changes in 25(OH)D.

Table 67. The relationship between vitamin D_3 daily doses and changes in 25(OH)D concentrations in RCTs (formerly Table 106) (updated from original report)

							Vit D_3 ± Ca Group			Placebo or Ca Group		
Author/Year	**Assay Method**	**Life stage**	**Base 25(OH)D, nmol/L**	**Vit D_3 Dose (IU/d)**	**Ca Dose (mg/d)**	**Duration (mo)**	**n**	**Mean Change From Baseline**	**SD**	**n**	**Mean Change From Baseline**	**SD**
New Studies												
Gaanmaa, 2012[278]	CLIA	9-18 yrs	17.8	800	0	6	57	31.9	11.1	55	9.6	9.7
Gepner, 2012[229]	HPLC	Postmenopausal	78.1 (26.5)	2500 Fortified cookies	0	4	55	39.2	23.2	55	-0.5	15.2
Islam, 2010[267]	RIA	19–50	36.1	400	600	12	40	32·1	23·6	35	0·5	13·8
Jorde, 2010[230]	RIA	19–50, 51–70	57.8	2857	500	12	104	42.8	22.5	112	-1.6	16.8
Jorde, 2010	RIA	19–50, 51–70	58.7	5,714	500	12	114	79.3	31.2	112	-1.6-	16.8
Karkainnen, 2010[269]	RIA	51–70, 70+	49.6	800	1000	36	287	24.7	24.1	306	6.8	19.3
Kukuljian, 2011[272]	RIA	51–70, 71+	88.1	Fortified milk 800	500	18	45	27.5	111.1	44	12.5	109.8
Li-Ng, 2009[150]	RRA	19–50, 51–70	63.7	2000	0	3	78	24.0	30.6	70	-2.1	20.9
Macdonald, 2013[245]	HPLC MS^2	51–70 yrs	34.6	400		12	84	31.6	19.8	89	-4.1	11.5
Macdonald. 2013	HPLC MS^2	51–70 yrs	34.5	1000		12	90	42.6	18.9	89	-4.1	11.5
Molgaard, 2010[248]	HPLC MS^2	9–11 yrs	42.6	200	0	12	73	11.0	10.3	74	−3.1	9.8
Molgaard, 2010	HPLC MS^2	9–11 yrs	40.0	400	0	12	74	13.3	10.8	74	-3.1	9.8
Nieves, 2012[244]	RIA	Postmenopause	29.0	1000	≤1000	24	55	26.0	41.4	48	1.0	12.5
Pfeiffer, 2009[186]	RIA	71+ yrs	54.5	800	1000	20	121	-7	17.1	121	-16	16.8
Salehpour, 2012[234]	ELISA	19–50 yrs	41.9 ()	1000	0	3	39	38·2	32	38	4·6	14
Salovaara, 2010[260]	RIA	51–70, 71+ yrs	49.5	800	1000	36	1586	24.6	20.5	1609	6.8	20.1
Toxqui, 2013[228]	ELISA	9–50 yrs	62.6	200		2	55	8.9	21.0	54	0.3	19.7
Wamberg, 2013[236]	HPLC MS^2	9–50 yrs	33.5	7000		6.5	22	77.2	18.4	21	12.8	15.0
Witham, 2013[235]	ELISA	9–71+ yrs	27	1667		2	25	10	10.2	25	0	10.2
Wood, 2012[231]	HPLC MS^2	Postmenopause	34.5	400	0	12	84	33.0	20.2	91	-2.7	12.4
Wood, 2012	HPLC MS^2	Postmenopause	30.3	1000	0	12	90	42.9	19.0	91	2.7	12.4
Zhu, 2010[188]	RIA	71+ yrs	44.7	D2: 1000	1000	12	129	14.7	13.3	132	0.8	13.2

Table 67. The relationship between vitamin D_3 daily doses and changes in 25(OH)D concentrations in RCTs (formerly Table 106) (updated from original report) (continued)

Author/Year	Assay Method	Life stage	Base 25(OH)D, nmol/L	Vit D_3 Dose (IU/d)	Ca Dose (mg/d)	Duration (mo)	Vit D_3 ± Ca Group			Placebo or Ca Group		
							n	Mean Change From Baseline	SD	n	Mean Change From Baseline	SD
Old Studies												
Bjorkman 2008[263]	HPLC	71+	23	400	0	6	60	26.5	11.8	59	1.9	10.2
Bjorkman 2008[263]	HPLC	71+	23	1200	0	6	63	49.1	19.5	59	1.9	10.2
Blum 2008[279]	ND	71+	73	700	500[A]	12	132	48.5	35.3	125	9.3	21.5
Bunout 2006[183]	RIA	71+	40	400	800[A]	9	46	33.4	14.3	46	3.5	10.0
Chapuy 1992[280]	RIA	71+	36	800	1200	18	73	65.0	16.5	69	-4.5	13.5
Chel 2008[281]	RIA	71+	23	600	0	4	46	46.9	15.4	45	0.3	12.2
Deroisy 2002[282]	RIA	71+	28	200	500[A]	3	50	14.7	10.0	50	4.5	10.0
Himmelstein 1990[283]	RRA	71+	45	2000	0	1.5	15	39.7	15.7	15	-2.7	13.4
Kenny 2003[284]	RRA	71+	62	1000	500[A]	6	29	22.3	10.1	31	-2.5	11.4
Krieg 1999[285]	RRA	71+	29	880	500	24	34	36.5	14.0	38	-15.0	11.1
Pfeifer 2000[286]	RIA	71+	25	880	1200[A]	2	74	40.5	27.0	74	18.3	20.9
Pfeifer 2001[238]	RIA	71+	25	800	1200	2	73	39.2	22.4	72	19.7	23.8
Sorva 1991[287]	RRA	71+	11	1000	1000	10	5	44.6	28.9	10	-1.4	2.3
Zhu 2008[275]	RIA	71+	68	1000	1200[A]	60	29	36.2	27.5	34	-2.9	27.4
Barnes 2006[288]	Not available	adults	52	600	1500[A]	2	12	38.6	15.1	15	-7.2	11.3
Bolton-Smith 2007[274]	RIA	adults	60	400	100	24	50	12.0	15.1	56	-8.2	14.3
Dawson-Hughes 1997[289]	RRA	adults	74	700	500	36	145	35.2	32.6	167	-2.1	22.7

Table 67. The relationship between vitamin D_3 daily doses and changes in 25(OH)D concentrations in RCTs (formerly Table 106) (updated from original report) (continued)

							Vit D_3 ± Ca Group			Placebo or Ca Group		
Author/Year	Assay Method	Life stage	Base 25(OH)D, nmol/L	Vit D_3 Dose (IU/d)	Ca Dose (mg/d)	Duration (mo)	n	Mean Change From Baseline	SD	n	Mean Change From Baseline	SD
Harris 2002[290]	HPLC/RRA	adults	55	800	0	2	27	22.3	14.0	23	-4.6	6.3
Heaney 2003[291]	RIA	adults	71	1000	0	5	16	12.0	16.0	16	-11.4	17.6
Heaney 2003[291]	RIA	adults	71	5000	0	5	17	91.9	37.6	16	-11.4	17.6
Heikkinen 1998[292]	HPLC/RRA	adults	26	300	500[A]	12	18	9.4	10.9	18	-3.3	6.4
Honkanen 1990[293]	Not available	adults	31	1800	1550	2.75	55	39.5	12.1	60	-13.1	9.2
Jensen 2002[294]	RRA	adults	41	400	1450	36	33	34.6	23.2	33	16.5	28.2
Nelson 2009[295]	RIA	adults	62	800	0	12	55	35.3	23.2	31	10.9	16.9
Orwoll 1988[296]	RRA	adults	58	1000	1000	12	46	25.0	19.1	46	3.0	19.1
Patel 2001[297]	RIA	adults	72	800	0	12	35	8.4	13.1	35	-9.2	12.8
Riis 1984[298]	Not available	adults	41	2000	500	12	8	87.5	14.1	7	-5.0	23.8
Trang 1998[299]	RIA	adults	42	4000	0	0.5	24	23.3	17.5	24	3.0	19.8
Chan 1982[300]	RRA	children	43	400	0	6	30	22.5	6.6	30	-2.5	6.6
El-Hajj (Fuleihan) 2006[48]	RRA	children	35	200	0	12	58	7.5	19.8	55	5.0	18.8
El-Hajj (Fuleihan) 2006[48]	RRA	children	35	2000	0	12	55	59.9	67.1	55	5.0	18.8

[A] Calcium supplement was given to all patients.

The format of this table has been slightly modifies to fit each RCT in one line. RRAs and RIAs represent multiple procedures or commercial assay kits.

Stratification of Key Outcomes by Vitamin D Assay Method

In addition to plotting the data for Vitamin D dose-response by the method used to assay serum 25(OH)D (Figure 15), for all outcomes reported in three or more RCTs or seven or more observational studies, we stratified the studies according to the assay method used to assess serum 25(OH)D concentrations (radioimmunoassay, radioreceptor/ligand assay, enzyme-linked immunoadsorption assay, chemiluminescence assay, and HPLC-tandem mass spectrometry). These stratified tables appear in Appendix H.

Outcomes for Tolerable Upper Intake Levels

We included only clinical outcomes of tolerable upper intake levels, such as all-cause mortality, cancer (incidence and mortality), soft tissue calcification, renal outcomes, and adverse events reported in RCTs.

Results of all-cause mortality and cancer have been described in previous sections. In brief, we did not find vitamin D and/or calcium associated with an increased risk of mortality. For cancer risk, there were some observational studies reporting high calcium intake may be associated with an increased risk of prostate cancer (see "Prostate cancer" in "Calcium and cancer" section). We did not identify any studies on soft tissue calcification and tolerable upper intake levels.

Renal Outcomes

As described in the original report, the WHI trial on women aged 50 to 79 years examined the effect of vitamin D_3 400 IU (the Recommended Dietary Allowance for women aged 50 to 70 years and below the 600 IU recommended intake for women > 70 years) in combination with 1000 mg calcium carbonate versus placebo and found an increase in the risk of renal stones (Hazard Ratio 1.17 95% CI 1.02, 1.34), corresponding to 5.7 events per 10,000 person years of exposure.[131] It should be noted that women in both groups were allowed to take additional vitamin D supplements up to 600 IU and later 1000 IU per day and calcium supplements up to 1000 mg per day. The baseline total calcium intakes (from foods and supplements) were high: 34% consumed less than 800 mg/d, 26% consumed 800 to 1200 mg/d, and 40% consumed more than 1200 mg/d. A prior publication from WHI trial provided the same data on the risk of renal stones was also included in the Ottawa EPC report.

No studies were identified **for the original report** that evaluated the effect of vitamin D, calcium, or combined vitamin D and calcium on other renal outcomes.

For the current report, two studies assessed the occurrence of nephrolithiasis among participants in RCTs that administered approximately 1100[201] and 2000IU[150] per day supplemental vitamin D without calcium. No incidents of nephrolithiasis were reported in either study.

Adverse Events Reported in RCTs

The reporting of adverse events in RCTs was generally inadequate, and most trials were not adequately powered to detect adverse events. Among the 63 RCTs included in the original report, 47 did not report information on adverse events. **Among 47 RCTs included in the current study, most did not include any information on adverse events.**

For the current report, one study, which administered 2000 or 4000IU per day to 504 pregnant women, reported no adverse events during the interventions.[42] Three studies reported on only one specific outcome, hypercalcemia/serum calcium, or reported on this outcome and stated no other AEs were reported.[1,187,239] Supplementation ranged from 400 to 5000IU per day in these studies; only 1 case of hypercalcemia was reported across all 4 of the studies, in a trial that administered 1000IU per day plus 1000mg calcium.[187] Seven other studies that assessed hypercalcemia also reported no cases.

Five studies reported on gastrointestinal symptoms,[150,151,235,236,269] of which only one included supplemental calcium. Two studies reported on serious adverse events, including one death, cancer diagnoses, and acute surgeries, which were more prevalent in the placebo group and thus could not have been related to the use of vitamin D.[152,201]

For the original report, five RCTs (in 6 publications) that enrolled a total of 444 subjects reported no adverse events during the trial periods.[48,96,290,301,302] Of these, one RCT administered combination of vitamin D_2 (1600 or 3600 IU/d) and vitamin D_3 (400 IU/d) supplements for 3 months, two RCTs administered vitamin D supplements (type of vitamin D not reported) with doses ranging from 200 to 2000 IU/d for 3 weeks or 1 year, one RCT used high-dose intermittent vitamin D_3 supplement (120,000 IU sachets given 3 times, every 2 weeks, for 6 weeks), and one RCT administered 1200 IU/d vitamin D_2 supplement for 5 years.

Eleven RCTs reported at least one adverse event (Table 68). Excessive gas, bloating, and gastrointestinal discomforts were reported to be associated with calcium supplementation (doses ranged from 600 to 1000 mg/d). Other RCTs of vitamin D (doses ranged from 400 to 5714 IU/d vitamin D_3 or ranged from 5000 to 10,000 vitamin D_2) and/or calcium supplementations (doses ranged from 200 to 1500 mg/d) reported few cases of gastrointestinal disruption (such as constipation, diarrhea, or upset stomach), musculoskeletal soreness, primary hyperparathyroidism, hypercalcemia, and renal calculi. One RCT reported some adverse events that required hospital admission, including retrosternal pain, a non-ST elevation myocardial infarction and a transient ischemic attack (all 3 cases in vitamin D 400 IU/d plus exercise training group) and one case of acute cholecystitis (in calcium, vitamin D plus exercise training group).[183] Another RCT reported that "there were no significant differences between the vitamin D and the control groups in the rate of incident cancer and vascular disease (ischemic heart disease and stroke)" (actual data not provided), and one participant died during the study.[247] However, these adverse events may or may not be associated with vitamin D and/or calcium supplementation in this study. Also described earlier in the "Renal outcomes" section, the WHI trial examined the effect of vitamin D_3 400 IU in combination with 1000 mg calcium carbonate versus placebo and found an increase in the risk of renal

stones (Hazard Ratio 1.17 95% CI 1.02, 1.34), corresponding to 5.7 events per 10,000 person years of exposure.[131]

Ottawa EPC Report

A total of 22 trials reported data on toxicity-related outcomes, 21 of which used doses above 400 IU/d. Toxicity results from trials with intakes of vitamin D above current reference intakes varied and this may have been related to different doses, baseline characteristics of populations or exposure times. Most trials excluded subjects with renal insufficiency or hypercalcemia, were of small sample sizes and had short durations of exposure to vitamin D. Event rates were low across trials in both the treatment and placebo arms.

Table 68. Adverse events reported in RCTs (formerly Table 107) (updated from original report)

Author Year	N Enrolled	Vit D Dose (IU/d)	Ca Dose (mg/d)	Duration	Adverse Event Data (N=Case#)
New Studies					
Wamberg[236]	52	7000IU/d	0	26 wks	Intervention group: 13 reports of side effects Control group: 17 reports of side effects Side effects included constipation, nausea, tiredness, and headache No participants developed symptomatic hypercalcemia
Witham[235]	50	100,000IU single dose	0	8 wks	Intervention group: 3 headaches, 1 complaint of diarrhea, 1 constipation, 1 urinary tract infection, 1 complaint of joint pains, 1 subconjunctival hemorrhage Control group: 2 headaches, 2 complaints of constipation, 1 vomiting, 1 diarrhea, 1 skin rash, 1 corneal ulcer, 1 menorrhagia, 1 chest wall pain, 1 insomnia No deaths, hospitalizations, or cases of hypercalcemia or renal calculi
Wagner[42]	504	2000, 4000IU/d	0	Throughout pregnancy	None found
Laaksi[151]	164	400IU/d	0	5 mos	Intervention group: 2 withdrawals because of stomach ache, nausea, diarrhea Control: 1 case facial rash
Karkainnen[269]	593	800IU/d	1000mg	3 yrs	17/290 withdrawals due to AEs: GI symptoms(9), exacerbation of diseases(2), mouth irritation, skin symptoms, nausea, cough, backache, weight increase (one each)
Prince[187]	302	1000IU/d	1000mg	1 yr	1 case mild hypercalcemia in intervention group
Holmund, 2012[239]	113	400, 1200, 1600IU/d	0	2.5 mos	No hypercalcemia in any arm; AEs assessed with pre-specified survey but none reported
Iuliano-Burns[242]	110	50,000IU/mo (~1600IU/d) vs. 50,000IU alternate months vs. single 50,000IU dose	0	1 yr	No cases of vitamin D toxicity or hypercalcemia

Table 68. Adverse events reported in RCTs (formerly Table 107) (updated from original report) (continued)

Author Year	N Enrolled	Vit D Dose (IU/d)	Ca Dose (mg/d)	Duration	Adverse Event Data (N=Case#)		
Li-Ng[150]	162	2000IU/d	0	3 mos	AE	Vitamin D	Placebo
					GI	7	6
					Musculoskeletal	5	5
					Chest pain	1	2
					Palpitations	1	0
					Infection	8	8
					Headache	2	0
					Dizziness	1	0
					Allergic rhinitis	10	6
					Falls	0	2
					Fatigue	2	1
					Skin changes	1	4
					Nephrolithiasis	0	0
					hypercalcemia	0	0
Lips[201]	226	8,000IU/week	0	4 mos	Clinical AEs	Vitamin D	Placebo
					One or more	24	26
					Serious	3	3
					Drug related	1	4
					Deaths	1	0
					Renal stones	0	0
Hollis 2011[1]	494	400, 2000, 4000IU/d	0	Up to 8 mos	No differences in serum calcium, no specific AEs reported		
Roth[44]	160	5000IU/d	0	3 mos	Neonatal clinical AEs: Serious nonfatal AEs: Vitamin D: 6 Placebo:7 Neonatal deaths: Vitamin D:1 Placebo: 3 Hypercalcemia: Vitamin D: 0 Placebo: 0		
Grimnis 2012[241]	297	800 IU/d vs. 20,000 IU 2x per week (average daily dose of 6,500	1000	1 yr	No difference in total AEs reported between groups or in organ-specific AEs, no significant difference in rate of hypercalcemia or hyperphosphatemia		
Murdoch[152]	322	200,000IU1st and 2nd month, 100,000IU monthly	0	18 mos	SAEs	Vitamin D	Placebo
					Cancer diagnosis/tx	4	1
					Surgical procedure Acute	3	5
					Elective	8	5
					Trauma	3	6
					Treatment for medical condition	3	2
					Hypercalcemia	0	0

Table 68. Adverse events reported in RCTs (formerly Table 107) (updated from original report) (continued)

Author Year	N Enrolled	Vit D Dose (IU/d)	Ca Dose (mg/d)	Duration	Adverse Event Data (N=Case#)
Original Studies					
Yamamoto 1995[303]	471	0	1000	6 mo	Comparing calcium group to the placebo group, excessive gas and bloating were more frequently reported by white women at 3 months and by whites, in general, at 6 months, and white men reported more loose stools at 6 months.
Moschonis 2006[276]	112	300 D_3	600 or 1200	12 mo	Bloating, constipation and intestinal discomfort apparently related to the calcium supplement
Bunout 2006[183]	96	400	800	9 mo	Adverse events that required hospital admission: Vit D plus exercise training group (n=3): retrosternal pain, a non-ST elevation myocardial infarction and a transient ischemic attack. Calcium, Vit D plus exercise training group (n=1): acute cholecystitis
Wactawski-Wende 2006[131]	36282	400	1000	7 y	The WHI trial found an increase in the risk of renal stones (Hazard Ratio 1.17 95% CI 1.02, 1.34), corresponding to 5.7 events per 10,000 person years of exposure.
Burleigh 2007[184]	205	800 D_3	1200	Median 1 mo	Hypercalcemia (n=2)
Lappe 2008[259]	5201	800	200	8 wks	GI disruption such as constipation, diarrhea, upset stomach (4%), and musculoskeletal soreness (0.9%)
Brooke 1980[47]	126	1000	0	3rd trimester only	Vit D group (hypocalcemia, n=0), placebo group (hypocalcemia, n=5)
Lappe 2007[102]	1180	1000 D_3	1400–1500	4 y	Renal calculi in placebo (n=1), renal calculi in calcium only (n=3), renal calculi in calcium plus vit D (n=1)
Mastaglia 2006[304]	65	5000 or 10,000 D_2	500	3 mo	Hypercalciuria (n=1) in control group
Zhu 2008[247]	256	1000 D_2	1200	12 mo	There were no significant differences between the vitamin D and the control groups in the rate of incident cancer and vascular disease (ischemic heart disease and stroke). There were 8 and 5 adverse events in vitamin D and the control groups, respectively. One participant in the vitamin D group had mild asymptomatic hypercalcemia one occasion. No case of renal calculus was reported. 1 participant was deceased during the study.

Table 68. Adverse events reported in RCTs (formerly Table 107) (updated from original report) (continued)

Author Year	N Enrolled	Vit D Dose (IU/d)	Ca Dose (mg/d)	Duration	Adverse Event Data (N=Case#)
Sneve 2008[95]	445	Group 1: 2 capsules of vitamin D_3 each 20,000 IU taken twice a week (Monday and Thursday): ~5714 IU/d Group 2: 1 capsules of vitamin D_3 each 20,000 IU taken twice a week (Monday and Thursday): ~2857 IU/d	500	12 mo	Primary hyperparathyroidism (n=2), increase in serum calcium to 2.62 mmol/L (n=1), transient increases in serum calcium > 2.59 mmol/L (n=4). 317 other adverse events were recorded, most of them related to GI discomfort. There were no significant differences between the treatment groups regarding adverse events.

Discussion

This evidence report on vitamin D and calcium in relation to health outcomes was prepared—**and subsequently updated**—for consideration by the Committee on Dietary Reference Intakes for Vitamin D and Calcium at the request of AHRQ on behalf of the various sponsors. This report does not make, nor was it intended to make, recommendations for DRI values concerning vitamin D or calcium. Responsibility for setting DRI values lies with the Committee. Evidence from systematic reviews is one of several types of information available to the Committee for use in its deliberations to establish DRI values. This is the first time that an independent systematic review is being commissioned to support the DRI process. Thus, it is important for users of this report to fully appreciate the nuances of the methodologies employed, as well as the strengths and limitations of this approach. In particular, it should be noted that total vitamin D exposure was not evaluated in this report because there is no valid method to quantify the contribution of endogenous vitamin D synthesis resulting from sun exposure and it is also the TEP's consensus that vitamin D intake, as estimated by current food frequency questionnaires, is too inaccurate to be of value.

The following statements in plain type derive from the original report. Statements pertaining to the current report follow those conclusions and are in boldface type. The original report identified 165 **(126 in the current report)** primary articles that met the eligibility criteria established by the TEP. In addition, **the original report** included 11 **(3 in the current report)** published systematic reviews that incorporated over 200 additional primary articles. Despite the relatively large number of studies included, with the following few exceptions, it is difficult to make any substantive and concise statements on the basis of the available evidence concerning the association of serum 25(OH)D concentration, supplemental vitamin D, dietary calcium intake, or the combination of both nutrients with the various health outcomes. It proved challenging because many of the studies contained substantial heterogeneity and their findings were inconsistent for the health outcomes examined. **The studies identified for the current report also were characterized by the same challenges.**

In general, among RCTs of hypertensive adults, calcium supplementation (400 to 2000 mg/d) lowered systolic, but not diastolic, blood pressure by a small but statistically significant amount (2 to 4 mm Hg). **Calcium supplementation alone was not considered for the current report.**

For body weight, despite a wide range of calcium intakes (from supplements or from dairy and nondairy sources) across the calcium trials, the RCTs were fairly consistent in finding no significant effect of increased calcium intake on body weight. **Body weight was not considered for the current report, with the exception of birth weight. The number of studies that reported birth weight was too small (both in size and volume) to make any statement regarding the effect of interventions of vitamin D with or without calcium on this outcome.**

For growth, a meta-analysis of 17 RCTs did not find a significant effect on weight and height gain attributable to calcium supplement in children ranged from 3 to 18 years of age. **Childhood growth was not considered as an outcome for the current report. The number of studies that reported prenatal growth as an outcome was too small to make any statements regarding the effect of interventions of vitamin D with or without calcium.**

For bone health, one well-conducted systematic review of RCTs found that vitamin D_3 (up to 800 IU/d) plus calcium (~500 mg/d) supplementation resulted in small increases in BMD of the spine, total body, femoral neck, and total hip in populations consisting predominantly of women in late menopause. **Of the studies identified for the current report, one of seven RCTs of vitamin D supplementation alone and six of seven RCTs of vitamin D plus calcium found**

increases in BMC/BMD: The study of vitamin D alone that reported a positive effect enrolled infants, whereas the studies of vitamin D and calcium primarily enrolled postmenopausal women; the study that reported no effect of administering both vitamin D and calcium enrolled only men.

For breast cancer, subgroup analyses in four cohort studies consistently found that calcium intake in the range of 780 to 1750 mg/d in premenopausal women was associated with a decreased risk for breast cancer. However, no RCTs of calcium supplementation to prevent breast cancer in premenopausal women have been published. In contrast, cohort studies of postmenopausal women are consistent in showing no association of calcium intake with the risk of breast cancer. **Studies of calcium alone were not included in the update report.**
For prostate cancer, three of four cohort studies found significant associations between higher calcium intake (>1500 or >2000 mg/day) and increased risk of prostate cancer, compared to men consuming lower amount of calcium (500–1000 mg/day). **Studies of calcium alone were not included in the update report.** For cardiovascular events, a cohort study and a nested case-control study found associations between lower serum 25(OH)D concentrations (less than either about 50 or 75 nmol/L) and increased risk of total cardiovascular events; however an RCT found no effect of supplementation and studies of specific cardiovascular events were too sparse to reach conclusions. **Studies identified for the current report that assessed associations between cardiovascular events and serum 25(OH)D concentrations reported inconsistent results.**

Taken together, six cohort studies of calcium intake suggest that in populations at relatively increased risk of stroke and with relatively low dietary calcium intake (i.e., in East Asia), lower levels of calcium intake under about 700 mg/day are associated with higher risk of stroke. This association, however, was not replicated in Europe or the United States, and one Finnish study found a possible association of increased risk of stroke in men with calcium intakes above 1000 mg. **Again, studies of calcium only were not included in the current report.**

Studies on the association between either serum 25(OH)D concentration or calcium intake and other forms of cancer (colorectal, pancreatic, prostate, all-cause); incidence of hypertension or specific cardiovascular disease events; immunologic disorders; and pregnancy-related outcomes including preeclampsia were either few in number or reported inconsistent findings. Too few studies of combined vitamin D and calcium supplementation have been conducted to allow adequate conclusions about its possible effects on health. The WHI trial was commonly the only evidence available for a given outcome. **One high-quality systematic review that included some of the studies reviewed in the original report and some in the current report found a significant association between lower serum 25(OH)D concentrations and increased risk for total cardiovascular disease and coronary heart disease risks.**

Strengths of This Report

The strengths of this report**—the original and the update—**lie in the wide range of topics covered, critical appraisal, detailed documentation, transparent methods to assess the scientific literature, and an unbiased selection of studies. A team of evidence-based methodologists not previously directly involved in research related to vitamin D and calcium worked with nutrient experts to refine the Key Questions (initially defined by AHRQ with input from various sponsors), analytic framework, and review criteria for the systematic review. After defining the questions and eligibility criteria with input from content experts and the sponsoring agencies, the Tufts EPC reviewed the published evidence on the topic. The intent was to perform a thorough

and unbiased systematic review of the literature base on available evidence as defined by prespecified criteria. Once the review process began, input from experts in the field was sought to clarify technical questions during the literature review process. These individuals did not participate in study selection or detailed data extraction from the included studies nor were any members serving on the IOM committee on vitamin D and calcium involved in the review of this document. A quality rating as detailed in the Methods chapter was assigned for each primary study and systematic review, and incorporated into the data summaries section of the report. On the basis of this work, a sound foundation has been created which will facilitate rapid and efficient future updates as needed.

Details concerning the process of question formulation, selection of health outcomes of interest, justification for study selection criteria, methods used for critical appraisals of studies and quality rating, and summary of results are described fully in the Methods chapter. This approach is critical to the establishment of a transparent and reproducible process. Furthermore, important variables that affect vitamin D status such as life stages, latitude of the study locale, background diet and skin pigmentation are documented in this review.

This evidence report was carried out under the AHRQ EPC program, which has a 12-year history of producing over 175 evidence reports and numerous technology assessments for various users including many federal agencies. EPCs are staffed by experienced methodologists who continuously refine approaches to conducting systematic reviews and develop new methods on the basis of accumulated experience encompassing a wide range of topics. In addition, **both the RAND and** the Tufts EPC have conducted a number of nutrition-related evidence reports,[23-26,305] **and Tufts** has conducted the mock exercise on vitamin A panel.[5] This report drew on these experiences, the expertise of the TEP, and the support of federal agencies.

DRI and the Literature on Vitamin D and Calcium

It should be emphasized that none of the studies reviewed were designed to address issues specifically relevant for establishing DRI values (i.e., to ascertain the optimal dose in a particular life stage to promote growth and tissue maintenance, and prevent chronic disease throughout the lifecycle). In general, the studies did not enroll subjects with ages that could be easily mapped to specific life stages as defined within the DRI framework (with the exception of postmenopausal women and pregnant or lactating women) and did not evaluate health outcomes on the basis of what doses will lower risk for a particular disease in prespecified life stages. Therefore, data will need to be extrapolated from these studies to craft a set of DRI values for vitamin D and calcium. This extrapolation may prove challenging.

Certain issues concerning the studies of vitamin D must be noted. As mentioned previously, it is difficult to evaluate nutritional adequacy because there are no methods currently available to quantify the contribution of endogenous vitamin D synthesis resulting from sun exposure on an individual or group level. In addition, it is generally accepted that estimating intake by dietary assessments is not a valid indicator of vitamin D status, because there are limitations in the completeness of nutrient databases for both food and dietary supplements vitamin D content and the rapidly changing landscape of vitamin D food fortification has not yet been captured in either instruments used to assess intake and the databases used to analyze the data. For example, vitamin D values are available for only about 600 out of 1400 foods in the USDA National Nutrient Database for Standard Reference (http://ndb.nal.usda.gov) and notably missing are foods recently fortified with vitamin D.[33] Given the recent trend towards increased nutrient fortification of the North American food supply, the lag in updating food composition tables, and

the inability to distinguish between fortified and unfortified foods when using most dietary assessment tools, it is difficult to accurately estimate dietary intakes of vitamin D, especially for a given year.

Shifts in methodological approaches to measure serum 25(OH)D concentrations, and the heterogeneous nature of the data available with respect to study locations (i.e., latitude) and times during the year (i.e., season) hamper our ability to succinctly summarize dose-response relationships. **The original report** did not perform a dose-response meta-analysis of the relationship between serum 25(OH)D concentrations and health outcomes because limited and inconsistent data would result in a meta-analysis that is difficult to interpret and results that may be misleading.

For the current study, we abstracted the methods used to assay serum 25(OH)D for all RCTs included in the assessment of dose-response, as well as the RCTs included in the original report. To track the assay methods more completely, we also noted the country and the year in which the assay was performed, when reported; however, very few studies reported the year assays were conducted. Combined with the evidence regarding the significant effect of season of blood draw on serum 25(OH)D concentrations, this lack of information on year of assay renders comparing or combining outcomes challenging, even when the same type of assay was used.

Furthermore, many of the large cohorts analyzed for associations of vitamin D with health outcomes enrolled mostly white participants aged approximately 40 to 70 years old and much of the data on intake dose-response and serum 25(OH)D concentration were derived from studies designed to measure bone health in postmenopausal women. These factors limit the applicability of the findings to other life stages and other racial groups.

Unlike serum 25(OH)D concentrations for vitamin D, there is no equivalent serum biomarker to indicate calcium status. Relying on dietary assessment to gauge calcium intake is limited by the confounding effect of vitamin D status on the efficiency of calcium absorption and uncertainties in the calcium content of many foods due to the recent trend in nutrient fortification of food, limited ability of current dietary assessment tools to distinguish among fortified and unfortified foods and the lag in updating nutrient databases with current nutrient information.

Limitations of Our Methodological Approach

The number of potentially relevant (English language articles on humans and not reviews) vitamin D studies indexed in MEDLINE is very large (~15,000) and the number of calcium studies is even larger (~110,000). **The searches conducted for the current report identified over 5,000 potentially relevant studies released since the completion of the original report in 2009.** Without unlimited time and resources, the systematic review conducted in this **report and the original** report had to focus on selected Key Questions predefined by our Federal sponsors with input from the IOM, and capitalize on existing systematic reviews. Using previous systematic reviews risks propagating deficiencies and errors[306] introduced in those reviews (e.g., errors in data abstraction, flawed assumptions in quantitative synthesis). Although we have assessed the quality of these systematic reviews using the AMSTAR[34] checklist, we cannot reliably know the validity of the reported summary data without knowing the details of the primary studies. It should also be stressed that a well-performed systematic review does not necessarily imply that the body of evidence for a particular outcome of interest is of high quality. While some systematic reviews assessed the quality of the individual studies, the methods used varied. Any systematic review is limited by the quality of the primary studies included in the

review. Unless the methods used to assess the quality of the primary studies is transparent and the details made available for examination, it would be difficult to reliably determine the validity of the conclusions. Also, relying on existing systematic reviews alone could have potentially precluded us from identifying all relevant studies because those systematic reviews might have addressed somewhat different questions and had a different scope from this review. For example, for growth outcomes in children, we principally relied on the findings from a meta-analysis of RCTs of calcium originally designed to evaluate bone density outcomes. If there were RCTs of calcium intake specifically designed to measure growth outcomes such as weight and height gain, but not bone density, then those studies would not have been identified. In addition, as per the task order from AHRQ, we relied on the Ottawa report for bone health outcomes and we did not examine specific studies included in that report. As a consequence, if those studies had reported other (than bone health) outcomes that were of interest, those studies would not have been included in this review.

As there is no consensus on how to assess the quality of the nutrition observational studies, we created a quality checklist based on a newly published reporting standard for observational studies[40] and nutrition reporting items that we believe should be considered in quality assessment. This checklist, however, has not been calibrated and the intra- and inter-rater variability have not been assessed. We should also remind readers that impeccable study reporting does not equate to study validity. However, transparent, comprehensive, and accurate reporting does help in evaluating a study's validity.

Also, studies on vitamin D and calcium were not specifically targeted at life stages (except for children, pregnant, and postmenopausal women) specified for the determination of DRIs. We, therefore, were unable to structure our report strictly according to pre-specified life stages. When a study enrolled populations that spanned multiple life stages, we provided our best estimates as to which life stage(s) the study's findings would be of most relevance.

Comments on the Observational Studies

All the included observational studies were designed to generate hypotheses of potential associations of multiple factors with vitamin D or calcium. Therefore, a finding of a significant association in these studies, after exploratory analyses, should not be considered equivalent to the result of studies that were designed to confirm this relationship. Many of the nested case-control studies typically excluded a substantial portion of participants (some as high as 60 to 70 percent) in the original cohorts because blood samples, or completed dietary questionnaires were not available. How this selection bias would affect the reported association is unclear. In addition, several of the studies might have suffered from outcome misclassification, for example, when cancer cases were identified from registries without histopathology verification. The effect of outcome misclassification is unpredictable. Furthermore, many of the studies did not report a power calculation. Even though many of the studies included cohorts with relatively large numbers of subjects (tens of thousands), it is plausible that, in fact, the included studies may have been underpowered to detect the true effect sizes. If that were the case, the significant effect reported may, in fact, be spurious. Furthermore, many of the reported effect sizes were small to moderate (with OR ranged from 1.03 to 2.0). When the effect size is small, the possibility of residual confounding by unmeasured variables must be considered.

Sources of Heterogeneity and Potential Biases

As has been mentioned previously, most of the findings reported in this review were inconsistent for each of the outcomes of interest. Many studies showed substantial heterogeneity. Some studies adjusted the serum 25(OH)D concentration by season of serum collection, some did not. While the majority of the studies used some form of immunoassay to measure the serum 25(OH)D concentration, a minority used competitive protein-binding assay**, and at least for the current report, some identified studies used HPLC/tandem mass spectrometry**. Some studies reported a substantial proportion of the frozen sera were accidentally thawed and limited the analyses that could be performed, **most studies omitted reporting the length of time between sample collection and assay, and studies differed regarding whether case (or intervention) samples and control samples were assayed simultaneously**. It is unclear how this heterogeneity of sample handling would alter the overall results. Many studies suffered from potentially inadequate outcome ascertainment (e.g., reliance on self-reported calcium intake and hypertension diagnosis). Time between measurement of serum 25(OH)D concentration and the diagnosis of interest also varied. For prostate and colorectal cancer, it ranged from 1 to more than 16 years. Factors potentially relevant to the outcomes of interest like family history (in colorectal cancer) were not consistently reported and accounted for in the studies. Also, the blinding of case assessors to the risk factor of interest (e.g., serum 25(OH)D concentrations) as well as that of investigators who measured the risk factor per se to outcomes were rarely reported.

The issue of compliance with supplement use is a major concern in interpreting the results of RCTs. This issue is exemplified by the results of two RCTs (reported in one article) on the effects of vitamin D supplementation during pregnancy on pregnancy complications, in which vitamin D supplementation itself was not associated with a lower risk for preeclampsia, but risk for preeclampsia was significantly associated with maternal serum 25(OH)D concentrations.[42] Similarly, accounting for adherence had a significant impact on the effect size for fracture risk reduction in the WHI.[2]

For studies on calcium supplementation, intake compliance, information on the bioavailability of the calcium source, the role of background sun exposure, and associated vitamin D effects were not consistently available across all studies. Thus, it is difficult to interpret those findings on an absolute level and among studies.

Finally, all systematic reviews, including this report, may suffer from potential publication and reporting biases since currently there is no reliable way to detect and correct these biases. However, there is an underlying suspicion of publication bias against studies having either null or negative outcomes and reporting bias toward “significant” outcomes in the literature.[243,244] Thus, it is important to consider these biases when reviewing the overall findings of any systematic review.

Vitamin D Intake and Response in Serum 25(OH)D Concentration

The findings of this review on the association between vitamin D intake dose and change in serum 25(OH)D concentration were derived from RCTs reviewed in a systematic review of bone health in postmenopausal women **and RCTs identified for (and included in) the current report that assessed outcomes of interest, most of which pertained to older populations**. This limits the applicability of the findings to other life stages. Though we did not find any reason to consider these trials to be biased, they are nonetheless an arbitrary sample of all studies that have reported the association between vitamin D intake dose and change in serum 25(OH)D

concentration. We did not perform a quantitative synthesis (e.g., meta-regression) to examine the relationship between vitamin D intake dose and serum 25(OH)D concentration due to the heterogeneity across studies. Studies had varied compliance rates in the vitamin D intake; limited or no adjustment for skin pigmentations, calcium intake, or background sun exposure; different vitamin D assay methodologies and measurement (both intra- and interassay) variability. All these factors increase the heterogeneity and limit the usefulness of an overall summary estimate for an intake dose response in serum 25(OH)D concentration. Nonetheless, overall, there appeared to be a trend for higher vitamin D supplementation dose resulting in higher net change in serum 25(OH)D concentration. **Furthermore, the current report identified a recent, quality systematic review/meta-analysis that examined this question in 75 RCTs and obtained similar results.**

Considerations for Future DRI Committees

Formulating the appropriate Key Questions is the most important aspect of conducting a systematic review to ensure the final product will meet the intended purpose. Ideally, this should be an iterative process involving the sponsors, EPC, TEP and targeted end-users. The questions should be reviewed and potentially refined once the "state" of the literature has been systematically appraised, with the understanding that any modifications to the Key Questions after the review process has started will likely extend the literature review and synthesis processes. In addition, developing relevant study selection criteria for the systematic review is critical to finding pertinent data to answer the Key Questions; the TEP should be engaged early in this process. Crafting a framework of the entire review process depicting the explicit roles of the sponsors, TEP, and targeted end-users could also be helpful for future reviews.

While the process of conducting the actual systematic review of a nutrient or group of nutrients on an agreed-upon set of Key Questions concerning specific health outcomes is carefully laid out and could be replicated without undue difficulty, the process of selecting which health outcomes would be important for inclusion in a systematic review could not be easily replicated. The health outcomes selected were decided after much deliberation by the TEP with input from the various partners. As the nature of the deliberation hinged much on the expertise reflected by the particular composition of the TEP, it is conceivable that a different TEP composed of members with different expertise may have recommended a different set of health outcomes for inclusion. To minimize this variability, an a priori designed set of instructions to weigh each outcome (taking into account factors like population attributable risk, morbidity, and others) for possible inclusion would be valuable.

References

1. Hollis BW, Johnson D, Hulsey TC, et al. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness.[Erratum appears in J Bone Miner Res. 2011 Dec; 26(12):3001]. J Bone Miner Res. 2011 Oct;26(10):2341-57. PMID: 21706518.
2. Prentice RL, Pettinger MB, Jackson RD, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int. 2013 Feb;24(2):567-80. PMID: 23208074.
3. Dietary reference intakes : the essential guide to nutrient requirements: Institute of Medicine (IOM). The National Academy Press; 2006.
4. The development of DRIs 1994-2004 : lessons learned and new challenges: workshop summary: Institute of Medicine (IOM). The National Academies Press. 2007.
5. Russell R, Chung M, Balk EM, et al. Opportunities and challenges in conducting systematic reviews to support the development of nutrient reference values: vitamin A as an example. Am J Clin Nutr. 2009 Mar;89(3):728-33. PMID: 19176732
6. Vitamin D and Health in the 21st Century: an Update. Proceedings of a conference held September 2007 in Bethesda, Maryland, USA. Am J Clin Nutr. 2008 Aug;88(2):483S-592S. PMID: 18788091
7. Yetley EA, Brule D, Cheney MC, et al. Dietary Reference Intakes for vitamin D: justification for a review of the 1997 values. Am J Clin Nutr. 2009 Mar;89(3):719-27. PMID: 19176741
8. Cranney A, Horsley T, O'Donnell S, et al. Effectiveness and safety of vitamin D in relation to bone health. EvidenceReport/Technology Assessment No.158 (Prepared by the University of Ottawa Evidence-basedPractice Center (UO-EPC) under Contract No.290-02-0021.AHRQ Publication No.07-E013. Aug 2007.
9. Chung M, Balk EM, Brendel M, et al. Vitamin D and Calcium: A Systematic Review of Health Outcomes. Evidence Report No. 183. (Prepared by the Tufts Evidence-based Practice Center under Contract No. HHSA 290-2007-10055-I.) AHRQ Publication No. 09-E015. Rockville, MD: Agency for Healthcare Research and Quality. August 2009 (183):1-420. PMID: 20629479.
10. Holick MF. Vitamin D deficiency. N Engl J Med. 2007 Jul;357(3):266-81. PMID: 17634462
11. DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr. 2004 Dec;80(6 Supple):1689S-96S. PMID: 15585789
12. Townsend K, Evans KN, Campbell MJ, et al. Biological actions of extra-renal 25-hydroxyvitamin D-1alpha-hydroxylase and implications for chemoprevention and treatment. J Steroid Biochem Mol Biol. 2005 Oct;97(1-2):103-9. PMID: 16081283
13. Norman AW. A vitamin D nutritional cornucopia: new insights concerning the serum 25-hydroxyvitamin D status of the US population. Am J Clin Nutr. 2008 Dec;88(6):1455-6. PMID: 19064502
14. Bikle D. Nonclassic actions of vitamin D. J Clin Endocrinol Metab. 2009 Jan;94(1):26-34. PMID: 18854395
15. White JH. Vitamin D signaling, infectious diseases, and regulation of innate immunity. Infect Immun. 2008 Sep;76(9):3837-43. PMID: 18505808
16. Mohr SB. A brief history of vitamin D and cancer prevention. Ann Epidemiol. 2009 Feb;19(2):79-83. PMID: 19185802
17. Dawson-Hughes B. Serum 25-hydroxyvitamin D and functional outcomes in the elderly. Am J Clin Nutr. 2008 Aug;88(2):537S-40S. PMID: 18689397
18. Buell JS, Dawson-Hughes B. Vitamin D and neurocognitive dysfunction: preventing "D"ecline? Mol Aspects Med. 2008 Dec;29(6):415-22. Epub 2008 May 13. PMID: 18579197.
19. Quarles LD. Endocrine functions of bone in mineral metabolism regulation. J Clin Invest. 2008 Dec;118(12):3820-8. PMID: 19033649

20. Hewison M. Vitamin D and innate immunity. Curr Opin Investig Drugs. 2008 May;9(5):485-90. PMID: 18465658

21. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. Mayo Clin Proc. 2013 Jul;88(7):720-55. PMID: 23790560.

22. Bucher HC, Guyatt GH, Cook DJ, et al. Users' guides to the medical literature: XIX. Applying clinical trial results. A. How to use an article measuring the effect of an intervention on surrogate end points. Evidence-Based Medicine Working Group. JAMA. 1999 Aug 25;282(8):771-8.

23. Balk E, Chung M, Chew P, et al. Effects of Soy on Health Outcomes. Evidence Report/Technology Assessment No. 26 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No 05-E024-2. Rockville, MD: Agency for Healthcare Research and Quality; 2005.

24. Balk E, Chung M, Raman G, et al. B Vitamins and Berries and Age-Related Neurodegenerative Disorders. Evidence Report/Technology Assessment No. 134 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No 06-E008. Rockville, MD: Agency for Healthcare Research and Quality; April 2006.

25. Balk E, Chung M, Lichtenstein A, et al. Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease. Evidence Report/Technology Assessment No. 93 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No. 04-E010-2. Rockville, MD: Agency for Healthcare Research and Quality; 2004.

26. Ip S, Chung M, Raman G, et al. Breastfeeding and Maternal and Infant Health Outcomes in Developed Countries. Evidence Report/Technology Assessment No. 153 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No 07-E007. Rockville, MD: April 2007.

27. Jordan H, Matthan N, Chung M, et al. Effects of omega-3 fatty acids on arrhythmogenic mechanisms in animal and isolated organ/cell culture studies. Evidence Report/Technology Assessment No. 92 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No. 04-E011-2. Rockville, MD: Agency for Healthcare Research and Quality; 2004.

28. Wang C, Chung M, Lichtenstein A, et al. Effects of Omega-3 Fatty Acids on Cardiovascular Disease. Evidence Report/Technology Assessment No. 94 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No. 04-E009-2. Rockville, MD: Agency for Healthcare Research and Quality; 2004.

29. Maclean CH, Newberry SJ, Mojica WA, et al. Effects of omega-3 fatty acids on cancer. Evid Rep Technol Assess (Summ). 2005 Feb;(113):1-4. PMID: 15777113.

30. Maclean CH, Issa AM, Newberry SJ, et al. Effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological diseases. [Review] [5 refs]. Evid Rep Technol Assess (Summ). 2005;(114):1-3. PMID: 15777112

31. Issa AM, Mojica WA, Morton SC, et al. The efficacy of omega-3 fatty acids on cognitive function in aging and dementia: a systematic review. [Review] [23 refs]. Dement Geriatr Cogn Disord. 2006;21(2):88-96. PMID: 16340205

32. Crandall CJ, Newberry SJ, Diamant A, et al. Treatment To Prevent Fractures in Men and Women With Low Bone Density or Osteoporosis: Update of a 2007 Report. Comparative Effectiveness Review No. 53. (Prepared by Southern California Evidence-based Practice Center under Contract No. 290-2001-10062-I.) Rockville (MD): Agency for Healthcare Research and Quality; March 2012. PMID: 22553885.

33. Holden JM, Lemar LE. Assessing vitamin D contents in foods and supplements: challenges and needs. Am J Clin Nutr. 2008 Aug;88(2):551S-3S. PMID: 18689400

34. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10. PMID: 1730298935.

35. Ballantyne JC, Carr DB, deFerranti S, et al. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. Anesth Analg. 1998;86(3):598-612. PMID: 9495424

36. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. PMID: 3802833

37. Higgins JP, Whitehead A, Turner RM, et al. Meta-analysis of continuous outcome data from individual patients. Stat Med. 2001 Aug 15;20(15):2219-41. PMID: 11468761

38. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003 9/6/2003;327(7414):557-60. PMID: 12958120

39. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Clin Oral Investig. 2003 Mar;7(1):2-7. PMID: 12673431

40. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007 Oct 20;370(9596):1453-7. PMID: 18064739.

41. Chung M, Balk EM, Ip S, et al. Reporting of systematic reviews of micronutrients and health: a critical appraisal. Am J Clin Nutr. 2009 Apr;89(4):1099-113. PMID: 19244363.

42. Wagner CL, McNeil RB, Johnson DD, et al. Health characteristics and outcomes of two randomized vitamin D supplementation trials during pregnancy: a combined analysis. Journal of Steroid Biochemistry & Molecular Biology. 2013 Jul;136:313-20. PMID: 23314242.

43. Kalra P, Das V, Agarwal A, et al. Effect of vitamin D supplementation during pregnancy on neonatal mineral homeostasis and anthropometry of the newborn and infant. Br J Nutr. 2012 Sep 28;108(6):1052-8. PMID: 22212646.

44. Roth DE, Al Mahmud A, Raqib R, et al. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: the AViDD trial. Nutr J. 2013 Apr 12;12(1):47. PMID: 23587190.

45. Burris HH, Rifas-Shiman SL, Camargo CA, Jr., et al. Plasma 25-hydroxyvitamin D during pregnancy and small-for-gestational age in black and white infants. Ann Epidemiol. 2012 Aug;22(8):581-6. PMID: 22658824.

46. Gernand AD, Simhan HN, Klebanoff MA, et al. Maternal serum 25-hydroxyvitamin D and measures of newborn and placental weight in a U.S. multicenter cohort study. J Clin Endocrinol Metab. 2013 Jan;98(1):398-404. PMID: 23162094.

47. Brooke OG, Brown IR, Bone CD, et al. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. BMJ. 1980 Mar 15;280(6216):751-4. PMID: 6989438

48. El-Hajj FG, Nabulsi M, Tamim H, et al. Effect of vitamin D replacement on musculoskeletal parameters in school children: a randomized controlled trial. J Clin Endocrinol Metab. 2006 Feb;91(2):405-12. PMID: 23810841

49. Feliciano ES, Ho ML, Specker BL, et al. Seasonal and geographical variations in the growth rate of infants in China receiving increasing dosages of vitamin D supplements. J Trop Pediatr. 1994 Jun;40(3):162-5. PMID: 8078115

50. Marya RK, Rathee S, Dua V, et al. Effect of vitamin D supplementation during pregnancy on foetal growth. Indian J Med Res. 1988 Dec;88:488-92. PMID: 3243609

51. Maxwell JD, Ang L, Brooke OG, et al. Vitamin D supplements enhance weight gain and nutritional status in pregnant Asians. BJOG. 1981 Oct;88(10):987-91. PMID: 6793058

52. Wagner CL, Hulsey TC, Fanning D, et al. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. Breastfeed Med. 2006;1(2):59-70. PMID: 17661565

53. Mallet E, Gugi B, Brunelle P, et al. Vitamin D supplementation in pregnancy: a controlled trial of two methods. Obstet Gynecol. 1986 Sep;68(3):300-4. PMID: 3755517

54. Marya RK, Rathee S, Lata V, et al. Effects of vitamin D supplementation in pregnancy. Gynecol Obstet Invest. 1981;12(3):155-61. PMID: 7239350

55. Gale CR, Robinson SM, Harvey NC, et al. Maternal vitamin D status during pregnancy and child outcomes. Eur J Clin Nutr. 2008 Jan;62(1):68-77. PMID: 17311057.

56. Morley R, Carlin JB, Pasco JA, et al. Maternal 25-hydroxyvitamin D and parathyroid hormone concentrations and offspring birth size. J Clin Endocrinol Metab. 2006 Mar;91(3):906-12. PMID: 16352684

57. Wang L, Song Y, Manson JE, et al. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circulation. Circ Cardiovasc Qual Outcomes. 2012 Nov;5(6):819-29. PMID: 23149428.

58. Bolland MJ, Bacon CJ, Horne AM, et al. Vitamin D insufficiency and health outcomes over 5 y in older women. Am J Clin Nutr. 2010 Jan;91(1):82-9. PMID: 19906799.

59. Messenger W, Nielson CM, Li H, et al. Serum and dietary vitamin D and cardiovascular disease risk in elderly men: a prospective cohort study. Nutr Metab Cardiovasc Dis. 2012 Oct;22(10):856-63. PMID: 21466949.

60. Welsh P, Doolin O, McConnachie A, et al. Circulating 25OHD, dietary vitamin D, PTH, and calcium associations with incident cardiovascular disease and mortality: the MIDSPAN Family Study. J Clin Endocrinol Metab. 2012 Dec;97(12):4578-87. PMID: 23071162.

61. Karakas M, Thorand B, Zierer A, et al. Low levels of serum 25-hydroxyvitamin D are associated with increased risk of myocardial infarction, especially in women: results from the MONICA/KORA Augsburg case-cohort study. J Clin Endocrinol Metab. 2013 Jan;98(1):272-80. PMID: 23150690.

62. Robinson-Cohen C, Hoofnagle AN, Ix JH, et al. Racial differences in the association of serum 25-hydroxyvitamin D concentration with coronary heart disease events. JAMA. 2013 Jul 10;310(2):179-88. PMID: 23839752.

63. Perna L, Schottker B, Holleczek B, et al. Serum 25-hydroxyvitamin d and incidence of fatal and nonfatal cardiovascular events: a prospective study with repeated measurements. J Clin Endocrinol Metab. 2013 Dec;98(12):4908-15. PMID: 24106288.

64. Hosseinpanah F, Yarjanli M, Sheikholeslami F, et al. Associations between vitamin D and cardiovascular outcomes; Tehran Lipid and Glucose Study. Atherosclerosis. 2011 Sep;218(1):238-42. PMID: 21676397.

65. Kuhn T, Kaaks R, Teucher B, et al. Plasma 25-hydroxyvitamin D and its genetic determinants in relation to incident myocardial infarction and stroke in the European prospective investigation into cancer and nutrition (EPIC)-Germany study. PLoS ONE [Electronic Resource]. 2013;8(7):e69080. PMID: 23935930.

66. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ. 2003 Mar;326(7387):469. PMID: 12609940

67. Wang TJ, Pencina MJ, Booth SL, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008 Jan;117(4):503-11. PMID: 18180395

68. Giovannucci E, Liu Y, Hollis BW, et al. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med. 2008 Jun 9;168(11):1174-80. PMID: 18541825.

69. Brondum-Jacobsen P, Benn M, Jensen GB, et al. 25-hydroxyvitamin d levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. Arterioscler Thromb Vasc Biol. 2012 Nov;32(11):2794-802. PMID: 22936341.

70. Eaton CB, Young A, Allison MA, et al. Prospective association of vitamin D concentrations with mortality in postmenopausal women: results from the Women's Health Initiative (WHI). Am J Clin Nutr. 2011 Dec;94(6):1471-8. PMID: 22030222.

71. Fiscella K, Franks P. Vitamin D, race, and cardiovascular mortality: findings from a national US sample. Ann Fam Med. 2010 Jan-Feb;8(1):11-8. PMID: 20065273.

72. Ginde AA, Scragg R, Schwartz RS, et al. Prospective study of serum 25-hydroxyvitamin D level, cardiovascular disease mortality, and all-cause mortality in older U.S. adults. J Am Geriatr Soc. 2009 Sep;57(9):1595-603. PMID: 19549021.

73. Pilz S, Dobnig H, Nijpels G, et al. Vitamin D and mortality in older men and women. Clin Endocrinol (Oxf). 2009 Nov;71(5):666-72. PMID: 19226272.

74. Signorello LB, Han X, Cai Q, et al. A prospective study of serum 25-hydroxyvitamin d levels and mortality among African Americans and non-African Americans. Am J Epidemiol. 2013 Jan 15;177(2):171-9. PMID: 23125439.

75. Tomson J, Emberson J, Hill M, et al. Vitamin D and risk of death from vascular and non-vascular causes in the Whitehall study and meta-analyses of 12,000 deaths. Eur Heart J. 2013 May;34(18):1365-74. PMID: 23257953.

76. Schottker B, Haug U, Schomburg L, et al. Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study. Am J Clin Nutr. 2013 Apr;97(4):782-93. PMID: 23446902.

77. Formiga F, Ferrer A, Megido MJ, et al. Low Serum Vitamin D is Not Associated with an Increase in Mortality in Oldest Old Subjects: The Octabaix Three-Year Follow-Up Study. Gerontology. 2014;60(1):10-5. PMID: 23689215.

78. Deo R, Katz R, Shlipak MG, et al. Vitamin D, parathyroid hormone, and sudden cardiac death: results from the Cardiovascular Health Study. Hypertension. 2011 Dec;58(6):1021-8. PMID: 22068871.

79. Hutchinson MS, Grimnes G, Joakimsen RM, et al. Low serum 25-hydroxyvitamin D levels are associated with increased all-cause mortality risk in a general population: the Tromso studyEur J Endocrinol. 2010 May;162(5):935-42. PMID: 20185562.

80. Jassal SK, Chonchol M, von Muhlen D, et al. Vitamin d, parathyroid hormone, and cardiovascular mortality in older adults: the Rancho Bernardo study.[Erratum appears in Am J Med. 2011 Oct;124(10):e9]. Am J Med. 2010 Dec;123(12):1114-20. PMID: 20870200.

81. Kestenbaum B, Katz R, de Boer I, et al. Vitamin D, parathyroid hormone, and cardiovascular events among older adults. J Am Coll Cardiol. 2011 Sep 27;58(14):1433-41. PMID: 21939825.

82. Kilkkinen A, Knekt P, Aro A, et al. Vitamin D status and the risk of cardiovascular disease death. Am J Epidemiol. 2009 Oct 15;170(8):1032-9. PMID: 19762371.

83. Lin S-W, Chen W, Fan J-H, et al. Prospective study of serum 25-hydroxyvitamin D concentration and mortality in a Chinese population. Am J Epidemiol. 2012 Dec 1;176(11):1043-50. PMID: 23139250.

84. Michaelsson K, Baron JA, Snellman G, et al. Plasma vitamin D and mortality in older men: a community-based prospective cohort study. Am J Clin Nutr. 2010 Oct;92(4):841-8. PMID: 20720256.

85. Melamed ML, Michos ED, Post W, et al. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Int Med. 2008 Aug 11;168(15):1629-37. PMID: 18695076

86. Skaaby T, Husemoen LL, Pisinger C, et al. Vitamin D status and incident cardiovascular disease and all-cause mortality: a general population study. Endocrine. 2013 Jun;43(3):618-25. PMID: 23015273.

87. de Boer IH, Levin G, Robinson-Cohen C, et al. Serum 25-hydroxyvitamin D concentration and risk for major clinical disease events in a community-based population of older adults: a cohort study.[Summary for patients in Ann Intern Med. 2012 May 1;156(9):I36; PMID: 22547485]. Ann Intern Med. 2012 May 1;156(9):627-34. PMID: 22547472.

88. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Vitamin D deficiency in postmenopausal, healthy women predicts increased cardiovascular events: a 16-year follow-up studyEur J Endocrinol. 2012 Oct;167(4):553-60. PMID: 22875588.

89. Marniemi J, Alanen E, Impivaara O, et al. Dietary and serum vitamins and minerals as predictors of myocardial infarction and stroke in elderly subjects. Nutr Metab Cardiovasc Dis. 2005 Jun;15(3):188-97. PMID: 15955467

90. Sun Q, Pan A, Hu FB, et al. 25-Hydroxyvitamin D levels and the risk of stroke: a prospective study and meta-analysis. Stroke. 2012 Jun;43(6):1470-7. PMID: 22442173.

91. Brodin E, Lerstad G, Grimnes G, et al. Serum levels of vitamin D are not associated with future risk of venous thromboembolism. The Tromso Study. Thromb Haemost. 2013 May;109(5):885-90. PMID: 23446951.

92. Brondum-Jacobsen P, Nordestgaard BG, Schnohr P, et al. 25-hydroxyvitamin D and symptomatic ischemic stroke: an original study and meta-analysis. Annals of Neurology. 2013 Jan;73(1):38-47. PMID: 23225498.

93. Semba RD, Houston DK, Bandinelli S, et al. Relationship of 25-hydroxyvitamin D with all-cause and cardiovascular disease mortality in older community-dwelling adults. J Clin Nutr. 2010 Feb;64(2):203-9. PMID: 19953106.

94. Heikkinen AM, Tuppurainen MT, Niskanen L, et al. Long-term vitamin D3 supplementation may have adverse effects on serum lipids during postmenopausal hormone replacement therapy. Eur J Endocrinol. 1997 Nov;137(5):495-502. PMID: 9405029

95. Sneve M, Figenschau Y, Jorde R. Supplementation with cholecalciferol does not result in weight reduction in overweight and obese subjectsEur J Endocrinol. 2008 Dec;159(6):675-84. PMID: 19056900.

96. Nagpal J, Pande JN, Bhartia A. A double-blind, randomized, placebo-controlled trial of the short-term effect of vitamin D3 supplementation on insulin sensitivity in apparently healthy, middle-aged, centrally obese men. Diabet Med. 2009 Jan;26(1):19-27. PMID: 19125756.

97. Ordonez-Mena JM, Schottker B, Haug U, et al. Serum 25-hydroxyvitamin d and cancer risk in older adults: results from a large German prospective cohort study. Cancer Epidemiol Biomarkers Prev. 2013 May;22(5):905-16. PMID: 23462913.

98. Cawthon PM, Parimi N, Barrett-Connor E, et al. Serum 25-hydroxyvitamin D, parathyroid hormone, and mortality in older men. J Clin Endocrinol Metab. 2010 Oct;95(10):4625-34. PMID: 20631024.

99. Afzal S, Bojesen SE, Nordestgaard BG. Low plasma 25-hydroxyvitamin D and risk of tobacco-related cancer. Clin Chem. 2013 May;59(5):771-80. PMID: 23503722.

100. Freedman DM, Looker AC, Abnet CC, et al. Serum 25-hydroxyvitamin D and cancer mortality in the NHANES III study (1988-2006). Cancer Res. 2010 Nov 1;70(21):8587-97. PMID: 20847342.

101. Fedirko V, Riboli E, Tjonneland A, et al. Prediagnostic 25-hydroxyvitamin D, VDR and CASR polymorphisms, and survival in patients with colorectal cancer in western European ppulations. Cancer Epidemiol Biomarkers Prev. 2012 Apr;21(4):582-93. PMID: 22278364.

102. Lappe JM, Travers-Gustafson D, Davies KM, et al. Vitamin D and calcium supplementation reduces cancer risk: results of a randomized trial. Am J Clin Nutr. 2007 Jun;85(6):1586-91. PMID: 17556697

103. Freedman DM, Looker AC, Chang SC, et al. Prospective study of serum vitamin D and cancer mortality in the United States. J Natl Cancer Inst. 2007 Nov 7;99(21):1594-602. PMID: 17971526

104. Barnett CM, Nielson CM, Shannon J, et al. Serum 25-OH vitamin D levels and risk of developing prostate cancer in older men. Cancer Causes Control. 2010 Aug;21(8):1297-303. PMID: 20383574.

105. Brandstedt J, Almquist M, Manjer J, et al. Vitamin D, PTH, and calcium and the risk of prostate cancer: a prospective nested case-control study. Cancer Causes Control. 2012 Aug;23(8):1377-85. PMID: 22706676.

106. Meyer HE, Robsahm TE, Bjorge T, et al. Vitamin D, season, and risk of prostate cancer: a nested case-control study within Norwegian health studies. Am J Clin Nutr. 2013 Jan;97(1):147-54. PMID: 23193007.

107. Park S-Y, Cooney RV, Wilkens LR, et al. Plasma 25-hydroxyvitamin D and prostate cancer risk: the multiethnic cohort. Eur J Cancer. 2010 Mar;46(5):932-6. PMID: 20064705.

108. Shui IM, Mucci LA, Kraft P, et al. Vitamin D-related genetic variation, plasma vitamin D, and risk of lethal prostate cancer: a prospective nested case-control study. J Natl Cancer Inst. 2012 May 2;104(9):690-9. PMID: 22499501.

109. Travis RC, Crowe FL, Allen NE, et al. Serum vitamin D and risk of prostate cancer in a case-control analysis nested within the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Epidemiol. 2009 May 15;169(10):1223-32. PMID: 19359375.

110. Ahn J, Peters U, Albanes D, et al. Serum vitamin D concentration and prostate cancer risk: a nested case-control study. J Natl Cancer Inst. 2008 Jun 4;100(11):796-804. PMID: 18505967.

111. Ahonen MH, Tenkanen L, Teppo L, et al. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). Cancer Causes Control. 2000 Oct;11(9):847-52. PMID: 11075874

112. Baron JA, Beach M, Wallace K, et al. Risk of prostate cancer in a randomized clinical trial of calcium supplementation. Cancer Epidemiol Biomarkers Prev. 2005 Mar;14(3):586-9. PMID: 15767334

113. Braun MM, Helzlsouer KJ, Hollis BW, et al. Prostate cancer and prediagnostic levels of serum vitamin D metabolites (Maryland, United States). Cancer Causes Control. 1995 May;6(3):235-9. PMID: 7612803

114. Corder EH, Guess HA, Hulka BS, et al. Vitamin D and prostate cancer: a prediagnostic study with stored sera. Cancer Epidemiol Biomarkers Prev. 1993 Sep;2(5):467-72. PMID: 8220092

115. Jacobs ET, Giuliano AR, Martinez ME, et al. Plasma levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and the risk of prostate cancer. J Steroid Biochem Mol Biol. 2004 May;89-90(1-5):533-7. PMID: 15225833

116. Li H, Stampfer MJ, Hollis JB, et al. A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. PLoS Medicine/Public Library of Science. 2007 Mar;4(3):e103. PMID: 17388667

117. Mikhak B, Hunter DJ, Spiegelman D, et al. Vitamin D receptor (VDR) gene polymorphisms and haplotypes, interactions with plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, and prostate cancer risk. Prostate. 2007 Jun 15;67(9):911-23. PMID: 17440943

118. Nomura AM, Stemmermann GN, Lee J, et al. Serum vitamin D metabolite levels and the subsequent development of prostate cancer (Hawaii, United States). Cancer Causes Control. 1998 Aug;9(4):425-32. PMID: 9794175

119. Platz EA, Leitzmann MF, Hollis BW, et al. Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and subsequent risk of prostate cancer. Cancer Causes Control. 2004 Apr;15(3):255-65. PMID: 15090720

120. Tuohimaa P, Tenkanen L, Ahonen M, et al. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int J Cancer. 2004 Jan;108(1):104-8. PMID: 14618623

121. Tuohimaa P, Tenkanen L, Syvala H, et al. Interaction of factors related to the metabolic syndrome and vitamin D on risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. 2007 Feb;16(2):302-7. PMID: 17301263

122. Gann PH, Ma J, Hennekens CH, et al. Circulating vitamin D metabolites in relation to subsequent development of prostate cancer. Cancer Epidemiol Biomarkers Prev. 1996 Feb;5(2):121-6. PMID: 8850273

123. Jenab M, Bueno-de-Mesquita HB, Ferrari P, et al. Association between pre-diagnostic circulating vitamin D concentration and risk of colorectal cancer in European populations:a nested case-control study. BMJ. 2010;340:b5500. PMID: 20093284.

124. Neuhouser ML, Manson JE, Millen A, et al. The influence of health and lifestyle characteristics on the relation of serum 25-hydroxyvitamin D with risk of colorectal and breast cancer in postmenopausal women. Am J Epidemiol. 2012 Apr 1;175(7):673-84. PMID: 22362582.

125. Woolcott CG, Wilkens LR, Nomura AMY, et al. Plasma 25-hydroxyvitamin D levels and the risk of colorectal cancer: the multiethnic cohort study. Cancer Epidemiol Biomarkers Prev. 2010 Jan;19(1):130-4. PMID: 20056631.

126. Lee JE, Li H, Chan AT, et al. Circulating levels of vitamin D and colon and rectal cancer: the Physicians' Health Study and a meta-analysis of prospective studies. Cancer Prev Res (Phila). 2011 May;4(5):735-43. PMID: 21430073.

127. Tangrea J, Helzlsouer K, Pietinen P, et al. Serum levels of vitamin D metabolites and the subsequent risk of colon and rectal cancer in Finnish men. Cancer Causes Control. 1997 Jul;8(4):615-25.

128. Otani T, Iwasaki M, Sasazuki S, et al. Plasma vitamin D and risk of colorectal cancer: the Japan Public Health Center-Based Prospective Study. Br J Cancer. 2007 Aug 6;97(3):446-51. PMID: 17622244

129. Wu K, Feskanich D, Fuchs CS, et al. A nested case control study of plasma 25-hydroxyvitamin D concentrations and risk of colorectal cancer. J Natl Cancer Inst. 2007 Jul 18;99(14):1120-9. PMID: 17623801

130. Feskanich D, Ma J, Fuchs CS, et al. Plasma vitamin D metabolites and risk of colorectal cancer in women. Cancer Epidemiol Biomarkers Prev. 2004 Sep;13(9):1502-8. PMID: 15342452

131. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006 Feb 16;354(7):684-96. PMID: 16481636

132. Garland CF, Comstock GW, Garland FC, et al. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. Lancet. 1989 Nov 18;2(8673):1176-8. PMID: 2572900

133. Braun MM, Helzlsouer KJ, Hollis BW, et al. Colon cancer and serum vitamin D metabolite levels 10-17 years prior to diagnosis. Am J Epidemiol. 1995 Sep 15;142(6):608-11. PMID: 7653469

134. Platz EA, Hankinson SE, Hollis BW, et al. Plasma 1,25-dihydroxy- and 25-hydroxyvitamin D and adenomatous polyps of the distal colorectum. Cancer Epidemiol Biomarkers Prev. 2000 Oct;9(10):1059-65. PMID: 11045788

135. Eliassen AH, Spiegelman D, Hollis BW, et al. Plasma 25-hydroxyvitamin D and risk of breast cancer in the Nurses' Health Study II. Breast Cancer Res. 2011;13(3):R50. PMID: 21569367.

136. McCullough ML, Stevens VL, Patel R, et al. Serum 25-hydroxyvitamin D concentrations and postmenopausal breast cancer risk: a nested case control study in the Cancer Prevention Study-II Nutrition Cohort. Breast Cancer Res. 2009;11(4):R64. PMID: 19715600.

137. Almquist M, Bondeson A-G, Bondeson L, et al. Serum levels of vitamin D, PTH and calcium and breast cancer risk-a prospective nested case-control study. Int J Cancer. 2010 Nov 1;127(9):2159-68. PMID: 20112341.

138. Engel P, Fagherazzi G, Boutten A, et al. Serum 25(OH) vitamin D and risk of breast cancer: a nested case-control study from the French E3N cohort. Cancer Epidemiol Biomarkers Prev. 2010 Sep;19(9):2341-50. PMID: 20826834.

139. Rejnmark L, Tietze A, Vestergaard P, et al. Reduced prediagnostic 25-hydroxyvitamin D levels in women with breast cancer: a nested case-control study. Cancer Epidemiol Biomarkers Prev. 2009 Oct;18(10):2655-60. PMID: 19789365.

140. Bertone-Johnson ER, McTiernan A, Thomson CA, et al. Vitamin D and calcium supplementation and one-year change in mammographic density in the women's health initiative calcium and vitamin D trial. Cancer Epidemiol Biomarkers Prev. 2012 Mar;21(3):462-73. PMID: 22253296.

141. Green AK, Hankinson SE, Bertone-Johnson ER, et al. Mammographic density, plasma vitamin D levels and risk of breast cancer in postmenopausal women. Int J Cancer. 2010 Aug 1;127(3):667-74. PMID: 19960434.

142. Bertone-Johnson ER, Chen WY, Holick MF, et al. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. Cancer Epidemiol Biomarkers Prev. 2005 Aug;14(8):1991-7. PMID: 16103450

143. Freedman DM, Chang S-C, Falk RT, et al. Serum levels of vitamin D metabolites and breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomarkers Prev. 2008 Apr;17(4):889-94. PMID: 18381472.

144. Jacobs ET, Thomson CA, Flatt SW, et al. Vitamin D and breast cancer recurrence in the Women's Healthy Eating and Living (WHEL) Study. Am J Clin Nutr. 2011 Jan;93(1):108-17. PMID: 20980485.

145. Kuhn T, Kaaks R, Becker S, et al. Plasma 25-hydroxyvitamin D and the risk of breast cancer in the European prospective investigation into cancer and nutrition: a nested case-control study. Int J Cancer. 2013 Oct 1;133(7):1689-700. PMID: 23526380.

146. Stolzenberg-Solomon RZ, Jacobs EJ, Arslan AA, et al. Circulating 25-hydroxyvitamin D and risk of pancreatic cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. Am J Epidemiol. 2010 Jul 1;172(1):81-93. PMID: 20562185.

147. Stolzenberg-Solomon RZ, Vieth R, Azad A, et al. A prospective nested case-control study of vitamin D status and pancreatic cancer risk in male smokers. Cancer Res. 2006 Oct 15;66(20):10213-9. PMID: 17047087

148. Stolzenberg-Solomon RZ, Hayes RB, Horst RL, et al. Serum vitamin D and risk of pancreatic cancer in the prostate, lung, colorectal, and ovarian screening trial. Cancer Res. 2009 Feb 15;69(4):1439-47. PMID: 19208842.

149. Manaseki-Holland S, Maroof Z, Bruce J, et al. Effect on the incidence of pneumonia of vitamin D supplementation by quarterly bolus dose to infants in Kabul: a randomised controlled superiority trial. Lancet. 2012 Apr 14;379(9824):1419-27. PMID: 22494826.

150. Li-Ng M, Aloia JF, Pollack S, et al. A randomized controlled trial of vitamin D3 supplementation for the prevention of symptomatic upper respiratory tract infections. Epidemiol Infect. 2009 Oct;137(10):1396-404. PMID: 19296870.

151. Laaksi I, Ruohola J-P, Mattila V, et al. Vitamin D supplementation for the prevention of acute respiratory tract infection: a randomized, double-blinded trial among young Finnish men. J Infect Dis. 2010 Sep 1;202(5):809-14. PMID: 20632889.

152. Murdoch DR, Slow S, Chambers ST, et al. Effect of vitamin D3 supplementation on upper respiratory tract infections in healthy adults: the VIDARIS randomized controlled trial. JAMA. 2012 Oct 3;308(13):1333-9. PMID: 23032549.

153. Belderbos ME, Houben ML, Wilbrink B, et al. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. Pediatrics. 2011 Jun;127(6):e1513-20. PMID: 21555499.

154. Camargo CA, Jr., Ingham T, Wickens K, et al. Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. Pediatrics. 2011 Jan;127(1):e180-7. PMID: 21187313.

155. Shin YH, Yu J, Kim KW, et al. Association between cord blood 25-hydroxyvitamin D concentrations and respiratory tract infections in the first 6 months of age in a Korean population: a birth cohort study (COCOA). Korean J Pediatr. 2013 Oct;56(10):439-45. PMID: 24244212.

156. Magnus MC, Stene LC, Haberg SE, et al. Prospective study of maternal mid-pregnancy 25-hydroxyvitamin D level and early childhood respiratory disorders. Paediatr Perinat Epidemiol. 2013 Nov;27(6):532-41. PMID: 24134527.

157. Thornton KA, Marin C, Mora-Plazas M, et al. Vitamin D deficiency associated with increased incidence of gastrointestinal and ear infections in school-age children. Pediatr Infect Dis J. 2013 Jun;32(6):585-93. PMID: 23340562.

158. Science M, Maguire JL, Russell ML, et al. Low serum 25-hydroxyvitamin D level and risk of upper respiratory tract infection in children and adolescents. Clin Infect Dis. 2013 Aug;57(3):392-7. PMID: 23677871.

159. Sabetta JR, DePetrillo P, Cipriani RJ, et al. Serum 25-hydroxyvitamin d and the incidence of acute viral respiratory tract infections in healthy adults. PLoS ONE [Electronic Resource]. 2010;5(6):e11088. PMID: 20559424.

160. Aregbesola A, Voutilainen S, Nurmi T, et al. Serum 25-hydroxyvitamin D3 and the risk of pneumonia in an ageing general population. J Epidemiol Community Health. 2013 Jun;67(6):533-6. PMID: 23596250.

161. Goldring ST, Griffiths CJ, Martineau AR, et al. Prenatal vitamin d supplementation and child respiratory health: a randomised controlled trial. PLoS ONE [Electronic Resource]. 2013;8(6):e66627. PMID: 23826104.

162. Jones AP, Palmer D, Zhang G, et al. Cord blood 25-hydroxyvitamin D3 and allergic disease during infancy. Pediatrics. 2012 Nov;130(5):e1128-35. PMID: 23090338.

163. Pike KC, Inskip HM, Robinson S, et al. Maternal late-pregnancy serum 25-hydroxyvitamin D in relation to childhood wheeze and atopic outcomes. Thorax. 2012 Nov;67(11):950-6. PMID: 22707522.

164. van Oeffelen AAM, Bekkers MBM, Smit HA, et al. Serum micronutrient concentrations and childhood asthma: the PIAMA birth cohort study. Pediatr Allergy Immunol. 2011 Dec;22(8):784-93. PMID: 21929603.

165. Tolppanen A-M, Sayers A, Granell R, et al. Prospective association of 25-hydroxyvitamin d3 and d2 with childhood lung function, asthma, wheezing, and flexural dermatitis. Epidemiology. 2013 Mar;24(2):310-9. PMID: 23377091.

166. Mai X-M, Langhammer A, Camargo CA, Jr., et al. Serum 25-hydroxyvitamin D levels and incident asthma in adults: the HUNT Study. Am J Epidemiol. 2012 Dec 15;176(12):1169-76. PMID: 23204497.

167. Racovan M, Walitt B, Collins CE, et al. Calcium and vitamin D supplementation and incident rheumatoid arthritis: the Women's Health Initiative Calcium plus Vitamin D trial. Rheumatolog Int. 2012 Dec;32(12):3823-30. PMID: 22190273.

168. Munger KL, Levin LI, Massa J, et al. Preclinical serum 25-hydroxyvitamin D levels and risk of type 1 diabetes in a cohort of US military personnel. Am J Epidemiol. 2013 Mar 1;177(5):411-9. PMID: 23380046.

169. Sorensen IM, Joner G, Jenum PA, et al. Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and risk of type 1 diabetes in the offspring. Diabetes. 2012 Jan;61(1):175-8. PMID: 22124461.

170. Salzer J, Hallmans G, Nystrom M, et al. Vitamin D as a protective factor in multiple sclerosis. Neurology. 2012 Nov 20;79(21):2140-5. PMID: 23170011.

171. Simpson M, Brady H, Yin X, et al. No association of vitamin D intake or 25-hydroxyvitamin D levels in childhood with risk of islet autoimmunity and type 1 diabetes: the Diabetes Autoimmunity Study in the Young (DAISY). Diabetologia. 2011 Nov;54(11):2779-88. PMID: 21858504

172. Wei SQ, Audibert F, Luo ZC, et al. Maternal plasma 25-hydroxyvitamin D levels, angiogenic factors, and preeclampsia. Am J Obstet Gynecol. 2013 May;208(5):390.e1-6. PMID: 23618499.

173. Scholl TO, Chen X, Stein TP. Vitamin D, secondary hyperparathyroidism, and preeclampsia. Am J Clin Nutr. 2013 Sep;98(3):787-93. PMID: 23885046.

174. Wei SQ, Audibert F, Hidiroglou N, et al. Longitudinal vitamin D status in pregnancy and the risk of pre-eclampsia. BJOG. 2012 Jun;119(7):832-9. PMID: 22462640.

175. Baker AM, Haeri S, Camargo CA, Jr., et al. A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia. J Clin Endocrinol Metab. 2010 Nov;95(11):5105-9. PMID: 20719829.

176. Woodham PC, Brittain JE, Baker AM, et al. Midgestation maternal serum 25-hydroxyvitamin D level and soluble fms-like tyrosine kinase 1/placental growth factor ratio as predictors of severe preeclampsia. Hypertension. 2011 Dec;58(6):1120-5. PMID: 21986503.

177. Shand AW, Nassar N, Von Dadelszen P, et al. Maternal vitamin D status in pregnancy and adverse pregnancy outcomes in a group at high risk for pre-eclampsia. BJOG. 2010 Dec;117(13):1593-8. PMID: 21040394.

178. Powe CE, Seely EW, Rana S, et al. First trimester vitamin D, vitamin D binding protein, and subsequent preeclampsia. Hypertension. 2010 Oct;56(4):758-63. PMID: 20733087.

179. Bodnar LM, Catov JM, Simhan HN, et al. Maternal vitamin D deficiency increases the risk of preeclampsia. J Clin Endocrinol Metab. 2007 Sep;92(9):3517-22. PMID: 17535985

180. Bodnar LM, Catov JM, Zmuda JM, et al. Maternal serum 25-hydroxyvitamin D concentrations are associated with small-for-gestational age births in white women. J Nutr. 2010 May;140(5):999-1006. PMID: 20200114.

181. Bodnar LM, Rouse DJ, Momirova V, et al. Maternal 25-hydroxyvitamin d and preterm birth in twin gestations. Obstet Gynecol. 2013 Jul;122(1):91-8. PMID: 23743453.

182. Baker AM, Haeri S, Camargo CA, Jr., et al. A nested case-control study of first-trimester maternal vitamin D status and risk for spontaneous preterm birth. Am J Perinatol. 2011 Oct;28(9):667-72. PMID: 21500145.

183. Bunout D, Barrera G, Leiva L, et al. Effects of vitamin D supplementation and exercise training on physical performance in Chilean vitamin D deficient elderly subjects. Exp Gerontol. 2006 Aug;41(8):746-52. PMID: 16797903

184. Burleigh E, McColl J, Potter J. Does vitamin D stop inpatients falling? A randomised controlled trial. Age Ageing. 2007 Sep;36(5):507-13. PMID: 8727400

185. Lyons RA, Johansen A, Brophy S, et al. Preventing fractures among older people living in institutional care: a pragmatic randomised double blind placebo controlled trial of vitamin D supplementation. Osteoporos Int. 2007 Jun;18(6):811-8. PMID: 17473911

186. Pfeifer M, Begerow B, Minne HW, et al. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int. 2009 Feb;20(2):315-22. PMID: 18629569.

187. Prince RL, Austin N, Devine A, et al. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. Arch Intern Med. 2008 Jan 14;168(1):103-8. PMID: 18195202.

188. Zhu K, Austin N, Devine A, et al. A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency. J Am Geriatr Soc. 2010 Nov;58(11):2063-8. PMID: 21054285.

189. Michael YL, Smit E, Seguin R, et al. Serum 25-hydroxyvitamin D and physical performance in postmenopausal women. J Womens Health (Larchmt). 2011 Nov;20(11):1603-8. PMID: 21923280.

190. Dam TTL, von Muhlen D, Barrett-Connor EL. Sex-specific association of serum vitamin D levels with physical function in older adults. Osteoporos Int. 2009 May;20(5):751-60. PMID: 18802657.

191. Scott D, Blizzard L, Fell J, et al. A prospective study of the associations between 25-hydroxy-vitamin D, sarcopenia progression and physical activity in older adults. Clin Endocrinol (Oxf). 2010 Nov;73(5):581-7. PMID: 20681994.

192. Houston DK, Tooze JA, Neiberg RH, et al. 25-hydroxyvitamin D status and change in physical performance and strength in older adults: the Health, Aging, and Body Composition Study. Am J Epidemiol. 2012 Dec 1;176(11):1025-34. PMID: 23118104.

193. Menant JC, Close JCT, Delbaere K, et al. Relationships between serum vitamin D levels, neuromuscular and neuropsychological function and falls in older men and women. Osteoporos Int. 2012 Mar;23(3):981-9. PMID: 21523392.

194. Barbour KE, Houston DK, Cummings SR, et al. Calciotropic hormones and the risk of hip and nonspine fractures in older adults: the Health ABC Study. J Bone Miner Res. 2012 May;27(5):1177-85. PMID: 22228250.

195. Cauley JA, Lacroix AZ, Wu L, et al. Serum 25-hydroxyvitamin D concentrations and risk for hip fractures.[Summary for patients in Ann Intern Med. 2008 Aug 19;149(4):I42; PMID: 18711151]. Ann Intern Med. 2008 Aug 19;149(4):242-50. PMID: 18711154.

196. Looker AC. Serum 25-hydroxyvitamin D and risk of major osteoporotic fractures in older U.S. adults. J Bone Miner Res. 2013 May;28(5):997-1006. PMID: 23184640.

197. Holvik K, Ahmed LA, Forsmo S, et al. Low serum levels of 25-hydroxyvitamin D predict hip fracture in the elderly: a NOREPOS study. J Clin Endocrinol Metab. 2013 Aug;98(8):3341-50. PMID: 23678033.

198. Barrett-Connor E, Laughlin GA, Li H, et al. The association of concurrent vitamin D and sex hormone deficiency with bone loss and fracture risk in older men: the osteoporotic fractures in men (MrOS) study. J Bone Miner Res. 2012 Nov;27(11):2306-13. PMID: 22777902.

199. Cauley JA, Danielson ME, Boudreau R, et al. Serum 25-hydroxyvitamin D and clinical fracture risk in a multiethnic cohort of women: the Women's Health Initiative (WHI). J Bone Miner Res. 2011 Oct;26(10):2378-88. PMID: 21710614.

200. Rouzi AA, Al-Sibiani SA, Al-Senani NS, et al. Independent predictors of all osteoporosis-related fractures among healthy Saudi postmenopausal women: the CEOR Study. Bone. 2012 Mar;50(3):713-22. PMID: 22178778.

201. Lips P, Binkley N, Pfeifer M, et al. Once-weekly dose of 8400 IU vitamin D(3) compared with placebo: effects on neuromuscular function and tolerability in older adults with vitamin D insufficiency. Am J Clin Nutr. 2010 Apr;91(4):985-91. PMID: 20130093

202. Ward KA, Das G, Roberts SA, et al. A randomized, controlled trial of vitamin D supplementation upon musculoskeletal health in postmenarchal females.[Erratum appears in J Clin Endocrinol Metab. 2010 Nov;95(11):5137]. J Clin Endocrinol Metab. 2010 Oct;95(10):4643-51. PMID: 20631020.

203. Burgi AA, Gorham ED, Garland CF, et al. High serum 25-hydroxyvitamin D is associated with a low incidence of stress fractures. J Bone Miner Res. 2011 Oct;26(10):2371-7. PMID: 21698667.

204. Autier P, Gandini S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch Intern Med. 2007 Sep 10;167(16):1730-7. PMID: 17846391

205. Avenell A, Gillespie WJ, Gillespie LD, et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev. 2008;(4). PMID: 24729336

206. Schleithoff SS, Zittermann A, Tenderich G, et al. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr. 2006 Apr;83(4):754-9. PMID: 16600924

207. Flicker L, MacInnis R, Stein M, et al. Should all older people in residential care receive Vitamin D to prevent falls? Results of a randomized trial. J Bone Miner Res. 2004;19(Suppl 1):S99. PMID: 16274368

208. Meyer HE, Smedshaug GB, Kvaavik E, et al. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. J Bone Miner Res. 2002 Apr;17(4):709-15. PMID: 11918228

209. Harwood RH, Sahota O, Gaynor K, et al. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NONOF) Study. Age Ageing. 2004 Jan;33(1):45-51. PMID: 14695863

210. Latham NK, Anderson CS, Lee A, et al. A randomized, controlled trial of quadriceps resistance exercise and vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). J Am Geriatr Soc. 2003 3/2003;51(3):291-9. PMID: 12588571

211. Johansson H, Oden A, Kanis J, et al. Low serum vitamin D is associated with increased mortality in elderly men: MrOS Sweden. Osteoporos Int. 2012 Mar;23(3):991-9. PMID: 22008880.

212. Kritchevsky SB, Tooze JA, Neiberg RH, et al. 25-Hydroxyvitamin D, parathyroid hormone, and mortality in black and white older adults: the health ABC study. J Clin Endocrinol Metab. 2012 Nov;97(11):4156-65. PMID: 22942386.

213. Smit E, Crespo CJ, Michael Y, et al. The effect of vitamin D and frailty on mortality among non-institutionalized US older adults. J Clin Nutr. 2012 Sep;66(9):1024-8. PMID: 22692022.

214. Szulc P, Claustrat B, Delmas PD. Serum concentrations of 17beta-E2 and 25-hydroxycholecalciferol (25OHD) in relation to all-cause mortality in older men--the MINOS study. Clin Endocrinol (Oxf). 2009 Oct;71(4):594-602. PMID: 19207314.

215. Szulc P, Maurice C, Marchand F, et al. Increased bone resorption is associated with higher mortality in community-dwelling men >or=50 years of age: the MINOS study. J Bone Miner Res. 2009 Jun;24(6):1116-24. PMID: 19113925.

216. Virtanen JK, Nurmi T, Voutilainen S, et al. Association of serum 25-hydroxyvitamin D with the risk of death in a general older population in Finland. Eur J Nutr. 2011 Aug;50(5):305-12. PMID: 20976461.

217. Wong YY, McCaul KA, Yeap BB, et al. Low vitamin D status is an independent predictor of increased frailty and all-cause mortality in older men: the Health in Men Study. J Clin Endocrinol Metab. 2013 Sep;98(9):3821-8. PMID: 23788685.

218. Sempos CT, Durazo-Arvizu RA, Dawson-Hughes B, et al. Is there a reverse J-shaped association between 25-hydroxyvitamin D and all-cause mortality? Results from the U.S. nationally representative NHANES. J Clin Endocrinol Metab. 2013 Jul;98(7):3001-9. PMID: 23666975.

219. Jia X, Aucott LS, McNeill G. Nutritional status and subsequent all-cause mortality in men and women aged 75 years or over living in the community. Br J Nutr. 2007 Sep;98(3):593-9. PMID: 17442130220.

220. Sambrook PN, Chen JS, March LM, et al. Serum parathyroid hormone is associated with increased mortality independent of 25-hydroxy vitamin d status, bone mass, and renal function in the frail and very old: a cohort study. J Clin Endocrinol Metab. 2004 Nov;89(11):5477-81. PMID: 15531500

221. Sambrook PN, Chen CJ, March L, et al. High bone turnover is an independent predictor of mortality in the frail elderly. J Bone Miner Res. 2006 Apr;21(4):549-55. PMID: 16598375

222. Visser M, Deeg DJ, Puts MT, et al. Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission. Am J Clin Nutr. 2006 Sep;84(3):616-22. PMID: 16960177

223. Anderson JL, May HT, Horne BD, et al. Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. Am J Cardiol. 2010 Oct 1;106(7):963-8. PMID: 20854958.

224. Wang L, Ma J, Manson JE, et al. A prospective study of plasma vitamin D metabolites, vitamin D receptor gene polymorphisms, and risk of hypertension in men. Eur J Nutr. 2013 Oct;52(7):1771-9. PMID: 23262750.

225. Forman JP, Giovannucci E, Holmes MD, et al. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension. Hypertension. 2007 May;49(5):1063-9. PMID: 17372031

226. Forman JP, Curhan GC, Taylor EN. Plasma 25-hydroxyvitamin D levels and risk of incident hypertension among young women. Hypertension. 2008 Nov;52(5):828-32. PMID: 18838623.

227. Forman JP, Scott JB, Ng K, et al. Effect of vitamin d supplementation on blood pressure in blacks. Hypertension. 2013 Apr;61(4):779-85. PMID: 23487599.

228. Toxqui L, Blanco-Rojo R, Wright I, et al. Changes in blood pressure and lipid levels in young women consuming a vitamin d-fortified skimmed milk: a randomised controlled trial. Nutrients. 2013 Dec;5(12):4966-77. PMID: 24317556.

229. Gepner AD, Ramamurthy R, Krueger DC, et al. A prospective randomized controlled trial of the effects of vitamin D supplementation on cardiovascular disease risk. PLoS ONE [Electronic Resource]. 2012;7(5):e36617. PMID: 22586483.

230. Jorde R, Sneve M, Torjesen P, et al. No improvement in cardiovascular risk factors in overweight and obese subjects after supplementation with vitamin D3 for 1 year. J Intern Med. 2010 May;267(5):462-72. PMID: 20141565.

231. Wood AD, Secombes KR, Thies F, et al. Vitamin D3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT. J Clin Endocrinol Metab. 2012 Oct;97(10):3557-68. PMID: 22865902.

232. Zhu W, Cai D, Wang Y, et al. Calcium plus vitamin D3 supplementation facilitated Fat loss in overweight and obese college students with very-low calcium consumption: a randomized controlled trial. Nutr J. 2013;12:8. PMID: 23297844.

233. Daly RM, Nowson CA. Long-term effect of calcium-vitamin D(3) fortified milk on blood pressure and serum lipid concentrations in healthy older men. Eur J Clin Nutr. 2009: 993-1000. PMID: 19156159

234. Salehpour A, Shidfar F, Hosseinpanah F, et al. Vitamin D3 and the risk of CVD in overweight and obese women: a randomised controlled trial. Br J Nutr. 2012 Nov 28;108(10):1866-73. PMID: 22317756.

235. Witham MD, Adams F, Kabir G, et al. Effect of short-term vitamin D supplementation on markers of vascular health in South Asian women living in the UK--a randomised controlled trial. Atherosclerosis. 2013 Oct;230(2):293-9. PMID: 24075759.

236. Wamberg L, Kampmann U, Stodkilde-Jorgensen H, et al. Effects of vitamin D supplementation on body fat accumulation, inflammation, and metabolic risk factors in obese adults with low vitamin D levels—results from a randomized trial. European J Intern Med. 2013 Oct;24(7):644-9. PMID: 23566943.

237. Scragg R, Khaw KT, Murphy S. Effect of winter oral vitamin D3 supplementation on cardiovascular risk factors in elderly adults. Euro J Clin Nutr. 1995 Sep;49(9):640-6. PMID: 7498100

238. Pfeifer M, Begerow B, Minne HW, et al. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab. 2001 Apr;86(4):1633-7. PMID: 11297596

239. Holmlund-Suila E, Viljakainen H, Hytinantti T, et al. High-dose vitamin d intervention in infants--effects on vitamin d status, calcium homeostasis, and bone strength. J Clin Endocrinol Metab. 2012 Nov;97(11):4139-47. PMID: 22933541.

240. Khadilkar AV, Sayyad MG, Sanwalka NJ, et al. Vitamin D supplementation and bone mass accrual in underprivileged adolescent Indian girls. Asia Pac J Clin Nutr. 2010;19(4):465-72. PMID: 21147706.

241. Grimnes G, Joakimsen R, Figenschau Y, et al. The effect of high-dose vitamin D on bone mineral density and bone turnover markers in postmenopausal women with low bone mass--a randomized controlled 1-year trial. Osteoporos Int. 2012 Jan;23(1):201-11. PMID: 21909730.

242. Iuliano-Burns S, Ayton J, Hillam S, et al. Skeletal and hormonal responses to vitamin D supplementation during sunlight deprivation in Antarctic expeditioners. Osteoporos Int. 2012 Oct;23(10):2461-7. PMID: 22215183.

243. Jorde R, Sneve M, Torjesen PA, et al. No significant effect on bone mineral density by high doses of vitamin D3 given to overweight subjects for one year. Nutr J. 2010;9:1. PMID: 20056003.

244. Nieves JW, Cosman F, Grubert E, et al. Skeletal effects of vitamin D supplementation in postmenopausal black women. Calcif Tissue Int. 2012 Nov;91(5):316-24. PMID: 22923289.

245. Macdonald HM, Wood AD, Aucott LS, et al. Hip bone loss is attenuated with 1000 IU but not 400 IU daily vitamin D3: a 1-year double-blind RCT in postmenopausal women. J Bone Miner Res. 2013 Oct;28(10):2202-13. PMID: 23585346.

246. Andersen R, Mølgaard C, Skovgaard LT, et al. Effect of vitamin D supplementation on bone and vitamin D status among Pakistani immigrants in Denmark: a randomised double-blinded placebo-controlled intervention study. The Br J Nutr. 2008:197-207. PMID: 18208636

247. Zhu K, Bruce D, Austin N, et al. Randomized controlled trial of the effects of calcium with or without vitamin D on bone structure and bone-related chemistry in elderly women with vitamin D insufficiency. J Bone Miner Res. 2008 Aug;23(8):1343-8. PMID: 18410225.

248. Molgaard C, Larnkjaer A, Cashman KD, et al. Does vitamin D supplementation of healthy Danish Caucasian girls affect bone turnover and bone mineralization? Bone. 2010 Feb;46(2):432-9. PMID: 19735754.

249. Hsia J, Heiss G, Ren H, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation. 2007 Feb 20;115(7):846-54. PMID: 17309935

250. LaCroix AZ, Kotchen J, Anderson G, et al. Calcium plus vitamin D supplementation and mortality in postmenopausal women: the Women's Health Initiative calcium-vitamin D randomized controlled trial. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2009 May;64(5):559-67. PMID: 19221190.

251. Caan B, Neuhouser M, Aragaki A, et al. Calcium plus vitamin D supplementation and the risk of postmenopausal weight gain. Arch Intern Med. 2007 May 14;167(9):893-902. PMID: 17502530

252. Major GC, Alarie F, Dore J, et al. Supplementation with calcium + vitamin D enhances the beneficial effect of weight loss on plasma lipid and lipoprotein concentrations. Am J Clin Nutr. 2007 Jan;85(1):54-9. PMID: 17209177

253. Brunner RL, Wactawski-Wende J, Caan BJ, et al. The effect of calcium plus vitamin D on risk for invasive cancer: results of the Women's Health Initiative (WHI) calcium plus vitamin D randomized clinical trial. Nutrition and cancer. 2011:827-41. PMID: 2177458254.

254. Ding EL, Mehta S, Fawzi WW, et al. Interaction of estrogen therapy with calcium and vitamin D supplementation on colorectal cancer risk: reanalysis of Women's Health Initiative randomized trial. Int J Cancer. 2008 Apr 15;122(8):1690-4. PMID: 18092326.

255. Grau MV, Baron JA, Sandler RS, et al. Vitamin D, calcium supplementation, and colorectal adenomas: results of a randomized trial. J Natl Cancer Inst. 2003 Dec 3;95(23):1765-71. PMID: 14652238

256. Chlebowski RT, Johnson KC, Kooperberg C, et al. Calcium plus vitamin D supplementation and the risk of breast cancer. J Natl Cancer Inst. 2008:1581-91. PMID: 19001601

257. Marya RK, Rathee S, Manrow M. Effect of calcium and vitamin D supplementation on toxaemia of pregnancy. Gynecol Obstet Invest. 1987;24(1):38-42. PMID: 3623260

258. Brunner RL, Cochrane B, Jackson RD, et al. Calcium, vitamin D supplementation, and physical function in the Women's Health Initiative. Journal of the American Dietetic Association. 2008:1472-9. PMID: 18755319

259. Lappe J, Cullen D, Haynatzki G, et al. Calcium and vitamin d supplementation decreases incidence of stress fractures in female navy recruits. J Bone Miner Res. 2008 May;23(5):741-9. PMID: 18433305.

260. Salovaara K, Tuppurainen M, Karkkainen M, et al. Effect of vitamin D(3) and calcium on fracture risk in 65- to 71-year-old women: a population-based 3-year randomized, controlled trial—the OSTPRE-FPS. J Bone Miner Res. 2010 Jul;25(7):1487-95. PMID: 20200964.

261. Kukuljan S, Nowson CA, Sanders K, et al. Effects of resistance exercise and fortified milk on skeletal muscle mass, muscle size, and functional performance in middle-aged and older men: an 18-mo randomized controlled trial. Journal of applied physiology (Bethesda). 2009:1864-73. PMID: 19850735

262. Karkkainen MK, Tuppurainen M, Salovaara K, et al. Does daily vitamin D 800 IU and calcium 1000 mg supplementation decrease the risk of falling in ambulatory women aged 65-71 years? A 3-year randomized population-based trial (OSTPRE-FPS). Maturitas. 2010 Apr;65(4):359-65. PMID: 20060665.

263. Björkman M, Sorva A, Risteli J, et al. Vitamin D supplementation has minor effects on parathyroid hormone and bone turnover markers in vitamin D-deficient bedridden older patients. Age and ageing. 2008:25-31. PMID: 17965037

264. Jackson RD, Lacroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med. 2006 Feb 16;354(7):669-83. PMID: 16481635

265. Margolis KL, Ray RM, Horn L, et al. Effect of calcium and vitamin D supplementation on blood pressure: the Women's Health Initiative Randomized Trial. Hypertension. 2008:847-55. PMID: 18824662

266. Zhu K, Greenfield H, Du X, et al. Effects of two years' milk supplementation on size-corrected bone mineral density of Chinese girls. Asia Pac J Clin Nutr. 2008:147-50. PMID: 18296324

267. Islam MZ, Shamim AA, Viljakainen HT, et al. Effect of vitamin D, calcium and multiple micronutrient supplementation on vitamin D and bone status in Bangladeshi premenopausal garment factory workers with hypovitaminosis D: a double-blinded, randomised, placebo-controlled 1-year intervention. Br J Nutr. 2010 Jul;104(2):241-7. PMID: 20193095.

268. Jackson RD, Wright NC, Beck TJ, et al. Calcium plus vitamin D supplementation has limited effects on femoral geometric strength in older postmenopausal women: the Women's Health Initiative. Calcif Tissue Int. 2011 Mar;88(3):198-208. PMID: 21253715.

269. Karkkainen M, Tuppurainen M, Salovaara K, et al. Effect of calcium and vitamin D supplementation on bone mineral density in women aged 65-71years: a 3-year randomized population-based trial (OSTPRE-FPS). Osteoporos Int. 2010 Dec;21(12):2047-55. PMID: 20204604.

270. Moschonis G, Katsaroli I, Lyritis GP, et al. The effects of a 30-month dietary intervention on bone mineral density: the Postmenopausal Health Study. Br J Nutr. 2010 Jul;104(1):100-7. PMID: 20370938.

271. Moschonis G, Kanellakis S, Papaioannou N, et al. Possible site-specific effect of an intervention combining nutrition and lifestyle counselling with consumption of fortified dairy products on bone mass: the Postmenopausal Health Study II. J Bone Miner Metab. 2011 Jul;29(4):501-6. PMID: 21455716.

272. Kukuljan S, Nowson CA, Sanders KM, et al. Independent and combined effects of calcium-vitamin D3 and exercise on bone structure and strength in older men: an 18-month factorial design randomized controlled trial. J Clin Endocrinol Metab. 2011 Apr;96(4):955-63. PMID: 21209030.

273. Cheng S, Lyytikainen A, Kroger H, et al. Effects of calcium, dairy product, and vitamin D supplementation on bone mass accrual and body composition in 10-12-y-old girls: a 2-y randomized trial. Am J Clin Nutr. 2005 Nov;82(5):1115-26. PMID: 16280447

274. Bolton-Smith C, McMurdo ME, Paterson CR, et al. Two-year randomized controlled trial of vitamin K1 (phylloquinone) and vitamin D3 plus calcium on the bone health of older women. J Bone Miner Res. 2007 Apr;22(4):509-19. PMID: 17243866

275. Zhu K, Devine A, Dick IM, et al. Effects of calcium and vitamin D supplementation on hip bone mineral density and calcium-related analytes in elderly ambulatory Australian women: a five-year randomized controlled trial. J Clin Endocrinol Metab. 2008 Mar;93(3):743-9. PMID: 18089701.

276. Moschonis G, Manios Y. Skeletal site-dependent response of bone mineral density and quantitative ultrasound parameters following a 12-month dietary intervention using dairy products fortified with calcium and vitamin D: the Postmenopausal Health Study. Br J Nutr. 2006 Dec;96(6):1140-8. PMID: 17181890

277. Autier P, Gandini S, Mullie P. A systematic review: influence of vitamin D supplementation on serum 25-hydroxyvitamin D concentration. J Clin Endocrinol Metab. 2012 Aug;97(8):2606-13. PMID: 22701014.

278. Ganmaa D, Giovannucci E, Bloom BR, et al. Vitamin D, tuberculin skin test conversion, and latent tuberculosis in Mongolian school-age children: a randomized, double-blind, placebo-controlled feasibility trial. Am J Clin Nutr. 2012 Aug;96(2):391-6. PMID: 22760564.

279. Blum M, Dallal GE, Dawson-Hughes B. Body size and serum 25 hydroxy vitamin D response to oral supplements in healthy older adults. J Am Coll Nutr. 2008 Apr;27(2):274-9. PMID: 18689559.

280. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med. 1992 Dec 3;327(23):1637-42. PMID: 1331788

281. Chel V, Wijnhoven HA, Smit JH, et al. Efficacy of different doses and time intervals of oral vitamin D supplementation with or without calcium in elderly nursing home residents. Osteoporos Int. 2008:663-71. PMID: 17874029

282. Deroisy R, Collette J, Albert A, et al. Administration of a supplement containing both calcium and vitamin D is more effective than calcium alone to reduce secondary hyperparathyroidism in postmenopausal women with low 25(OH)vitamin D circulating levels. Aging Clin Exp Res. 2002 Feb;14(1):13-7. PMID: 12027147

283. Himmelstein S, Clemens TL, Rubin A, et al. Vitamin D supplementation in elderly nursing home residents increases 25(OH)D but not 1,25(OH)2D. Am J Clin Nutr. 1990 Oct;52(4):701-6. PMID: 2403063

284. Kenny AM, Biskup B, Robbins B, et al. Effects of vitamin D supplementation on strength, physical function, and health perception in older, community-dwelling men. J Am Geriatr Soc. 2003 Dec;51(12):1762-7. PMID: 14687355

285. Krieg MA, Jacquet AF, Bremgartner M, et al. Effect of supplementation with vitamin D3 and calcium on quantitative ultrasound of bone in elderly institutionalized women: a longitudinal study. Osteoporos Int. 1999 1999;9(6):483-8. PMID: 10624454

286. Pfeifer M, Begerow B, Minne HW, et al. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res. 2000 Jun;15(6):1113-8. PMID: 10841179

287. Sorva A, Risteli J, Risteli L, et al. Effects of vitamin D and calcium on markers of bone metabolism in geriatric patients with low serum 25-hydroxyvitamin D levels. Calcif Tissue Int. 1991;49 Suppl:S88-S9. PMID: 1933612

288. Barnes MS, Robson PJ, Bonham MP, et al. Effect of vitamin D supplementation on vitamin D status and bone turnover markers in young adults. Eur J Clin Nutr. 2006 Jun;60(6):727-33. PMID: 16391584

289. Dawson-Hughes B, Harris SS, Krall EA, et al. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med. 1997 Sep 4;337(10):670-6. PMID: 9278463

290. Harris SS, Dawson-Hughes B. Plasma vitamin D and 25OHD responses of young and old men to supplementation with vitamin D3. J Am Coll Nutr. 2002 Aug;21(4):357-62. PMID: 12166534

291. Heaney RP, Davies KM, Chen TC, et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr. 2003 Jan;77(1):204-10. PMID: 12499343

292. Heikkinen A, Parviainen MT, Tuppurainen MT, et al. Effects of postmenopausal hormone replacement therapy with and without vitamin D3 on circulating levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. Calcif Tissue Int. 1998 Jan;62(1):26-30. PMID: 9405729

293. Honkanen R, Alhava E, Parviainen M, et al. The necessity and safety of calcium and vitamin D in the elderly. J Am Geriatr Soc. 1990 Aug;38(8):862-6. PMID: 2387950

294. Jensen C, Holloway L, Block G, et al. Long-term effects of nutrient intervention on markers of bone remodeling and calciotropic hormones in late-postmenopausal women. Am J Clin Nutr. 2002 Jun;75(6):1114-20. PMID: 12036821

295. Nelson ML, Blum JM, Hollis BW, et al. Supplements of 20 microg/d cholecalciferol optimized serum 25-hydroxyvitamin D concentrations in 80% of premenopausal women in winter. J Nutr. 2009 Mar;139(3):540-6. PMID: 19158226.

296. Orwoll ES, Weigel RM, Oviatt SK, et al. Calcium and cholecalciferol: effects of small supplements in normal men. Am J Clin Nutr. 1988 Jul;48(1):127-30. PMID: 2839025

297. Patel R, Collins D, Bullock S, et al. The effect of season and vitamin D supplementation on bone mineral density in healthy women: a double-masked crossover study. Osteoporos Int. 2001;12(4):319-25. PMID: 11420782

298. Riis B, Christiansen C, Rodbro P. The effect of different vitamin D treatments on serum vitamin D levels in early postmenopausal women. Acta Vitaminol Enzymol. 1984;6(2):77-82. PMID: 6093487

299. Trang HM, Cole DE, Rubin LA, et al. Evidence that vitamin D3 increases serum 25-hydroxyvitamin D more efficiently than does vitamin D2. Am J Clin Nutr. 1998 Oct;68(4):854-8. PMID: 9771862

300. Chan GM, Roberts CC, Folland D, et al. Growth and bone mineralization of normal breast-fed infants and the effects of lactation on maternal bone mineral status. Am J Clin Nutr. 1982 Sep;36(3):438-43. PMID: 7113949

301. Basile LA, Taylor SN, Wagner CL, et al. The effect of high-dose vitamin D supplementation on serum vitamin D levels and milk calcium concentration in lactating women and their infants. Breastfeed Med. 2006;1(1):27-35. PMID: 17661558

302. Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr. 2004 Dec;80(6 Suppl):1752S-8S. PMID: 15585800

303. Yamamoto ME, Applegate WB, Klag MJ, et al. Lack of blood pressure effect with calcium and magnesium supplementation in adults with high-normal blood pressure. Results from Phase I of the Trials of Hypertension Prevention (TOHP). Trials of Hypertension Prevention (TOHP) Collaborative Research Group. Ann Epidemiol. 1995 Mar;5(2):96-107. PMID: 7795837

304. Mastaglia SR, Mautalen CA, Parisi MS, et al. Vitamin D2 dose required to rapidly increase 25OHD levels in osteoporotic women. Eur J Clin Nutr. 2006 May;60(5):681-7. PMID: 16391587

305. Bonis PA, Chung M, Tatsioni A, et al. Effects of omega-3 fatty acids on organ transplantation. Evidence Report/Technology Assessment No. 115 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No. 05-E012-2. Rockville, MD: Agency for Healthcare Research and Quality; 2005.

306. Whitlock EP, Lin JS, Chou R, et al. Using existing systematic reviews in complex systematic reviews. Ann Int Med. 2008 May 20;148(10):776-82. PMID: 18490690

307. Turpeinen U, Hohenthal U, Stenman U-H. Determination of 25-Hydroxyvitamin D in Serum by HPLC and Immunoassay. Clin Chem. 2003;49(9):1521-4. PMID: 12928235

308. Haddad JG, Chyu KJ. Competitive Protein-Binding Radioassay for 25-Hydroxycholecalciferol. J Clin Endocrinol Metab. 1971;33(6):992-5. PMID: 4332615

309. Preece MA, O'Riordan JLH, Lawson DEM, et al. A Competitive Protein-Binding Assay for 25-Hydroxycholecalciferol and 25-Hydroxyergocalciferol in Serum. Clinica Chimica Acta. 1974;54:235-42. PMID: 4546706

310. Reinhardt TA, Horst RL, Orf JW, et al. A Microassay for 1,25-Dihydroxyvitamin D Not Requiring High Performance Liquid Chromatography: Application to Clinical Studies. J Clin Endocrinol Metab. 1984;58(1):91-8. PMID: 6605973

311. Parviainen MT, Savolainen KE, Korhonen PH, et al. An improved method for routine determination of vitamin D and its hydroxylated metabolites in serum from children and adults. Clinica Chimica Acta. 1981;114:233-47. PMID: 6974620

312. Belsey R, Deluca HF, Potts JTJ. Competitive binding assay for vitamin D and 25-OH vitamin D. J Clinical Endocrinol Metab. 1971;33(3):554-7. PMID: 4328344

313. Redhwi AA, C. AD, Smith GN. A simple method for the isolation of vitamin D metabolites from plasma extracts. Steroids. 1982;39(2):149-54. PMID: 6280344

314 orman AW, Bishop JE, Jongen M. Measurements of vitamin D metabolites. Endocrine control of bone and calcium metabolism. Amsterdam: Elsevier; 1984:7-10. PMID: 3034157

315. Shepard RM, Horst RL, Hamstra AJ, et al. Determination of vitamin D and its metabolites in plasma from normal and anephric man. Biochem J. 1979;182(1):55-69. PMID: 227368

316. Pettifor JM, Ross FP, Wang J. A competitive protein-binding assay for 25-hydroxyvitamin D. Clin Sci Mol Med Suppl. 1976;51(6):605-7. PMID: 1070425

317. Binkley N, Drezner MK, Hollis BW. Laboratory reporting of 25-hydroxyvitamin D results: potential for clinical misinterpretation. Clin Chem. 2006;52(11):2124-5. PMID: 17068180

318. Lensmeyer GL, Wiebe DA, Binkley N, et al. HPLC method for 25-hydroxyvitamin D measurement: comparison with contemporary assays. Clin Chem. 2006;52(6):1120-6. PMID: 16574756

319. Jakobsen J, Bysted A, Andersen R, et al. Vitamin D status assessed by a validated HPLC method: within and between variation in subjects supplemented with vitamin D3. Scand J Clin Lab Invest. 2009;69(2):190-7. PMID: 18942019

320. Maunsell Z, Wright DJ, Rainbow SJ. Routine isotope-dilution liquid chromatography-tandem mass spectrometry assay for simultaneous measurement of the 25-hydroxy metabolites of vitamins D2 and D3. Clin Chem. 2005 Sep;51(9):1683-90. PMID: 16020493.

Abbreviations

$1,25(OH)_2D$	Calcitriol
25(OH)D	25-hydroxyvitamin D
AHRQ	Agency for Healthcare Research and Quality
AMSTAR	Assessment of multiple systematic reviews
Anthrop	Anthropometric measures
ASA	Acetyl-salicylic acid (aspirin)
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
BCDDP	Breast Cancer Detection Demonstration Project
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
Ca	Calcium
CABG	Coronary artery bypass graft
CeVD	Cerebrovascular disease
CHD	Coronary heart disease
CI	Confidence Interval
CIFOS	Calcium Intake Fracture Outcome Study
CONSORT	Consolidated Standards of Reporting Trials
CPBA	Competitive protein binding assay
CPEP	Calcium for Prevention of Preeclampsia Trial
CPP	Calcium Polyp Prevention Study
CPS	Cancer Prevention Study
CRC	Colorectal cancer
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
Demograph	Demographics
Dx	Diagnosis
DM	Diabetes Mellitus
DRI	Dietary Reference Intake
Dx	Diagnosis
EAR	Estimated average requirement
EPC	Evidence-based Practice Center
FFQ	Food frequency questionnaire
FNB	Food and Nutrition Board
FOS	Framingham Offspring Study
FREE	Fracture Risk Epidemiology in the Elderly
HAH	Harvard Alumni Health Study
HbC	Hemoglobin C disease
HPFS	Health Professionals Followup Study
HPLC	High pressure liquid chromatography
HR	Hazard ratio
ht	Height
HT	Hormone (replacement) therapy
HTN	Hypertension
IA	Islet Autoimmune

IHD	Ischemic heart disease
IOM	Institute of Medicine
Iowa WHS	Iowa Women's Health Study
IQR	Interquartile range
IU	International unit
Japan CC	Japan Collaborative Cohort
Japan PHC	Japan Public Health Center study
Kupio ORFPS	Kupio Osteoporosis Risk Factor and Prevention Study
MCS	Multiethnic Cohort Study, Hawaii, California
MI	Myocardial infarction
mil	Million
mo	Months(s)
MS	Multiple sclerosis
N	Number of subjects
n	Number of subjects had event(s)
NA	Not applicable
nd	No data
NHANES	National Health and Nutrition Examination Survey
NHEFS	NHANES I Epidemiologic Followup Study
NHS	Nurses' Health Study
NIH	National Institutes of Health
NIH-AARP	National Institutes of Health—American Association of Retired Persons
NPC	Nutrition Prevention of Cancer trial
NS	Not significant
ODS	Office of Dietary Supplements
OR	Odds Ratio
OS	Observational Study
PAHSG	Princess Anne Hospital Study Group, U.K.
PCI	Percutaneous coronary intervention
PHS	Physicians' Health Study
PI(E)CO	Population, Intervention (or Exposure), Comparison and Outcome
PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
PMID	PubMed (unique) identifier
PSA	Prostate specific antigen
PTH	Parathyroid hormone
RA	Rheumatoid arthritis
RCT	Randomized-controlled trial
RDA	Recommended dietary allowance
RIA	Radioimmunoassay
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGA	Small-for-gestational-age
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
Subgp	Subgroup

Suppl	Supplement(s)
TEP	Technical Expert Panel
TIA	Transient ischemic attack
TOHP	Trials of Hypertension Prevention
TOO	Task order officer
UK	United Kingdom
UL	Tolerable upper intake levels
U.S.	United States
USDA	United States Department of Agriculture
UV	Ultraviolet rays
Vit	Vitamin
WCC	Washington County Cohort
WHI	Women's Health Initiative
WHS	Women's Health Study
wk	week(s)
WMD	Weighted mean difference
wt	Weight
y	Year(s)

Latitudes of Selected Cities

Latitude	Western Hemisphere	Eastern Hemisphere
64° N	Reykjavik, Iceland Nome, Alaska	
60-61° N	Anchorage, Alaska	Oslo, Norway
56° N		Copenhagen, Denmark
52° N		Berlin, Germany Amsterdam, Netherlands
51° N	Calgary, Alberta	London, England
49° N	Vancouver, British Columbia	Paris, France
48° N	Seattle, Washington	Munich, Germany
47° N	Quebec City, Quebec Bismarck, North Dakota	Zurich, Switzerland
45° N	Ottawa, Ontario Minneapolis, Minnesota	Milan, Italy
44° N	Toronto, Ontario Portland, Maine	
42° N	Boston, Massachusetts Chicago, Illinois	Rome, Italy
41° N	New York, New York Salt Lake City, Utah	Barcelona, Spain
40° N	Philadelphia, Pennsylvania Columbus, Ohio	Madrid, Spain Beijing, China
39° N	Washington, DC St Louis, Missouri Sacramento, California	
38° N	Louisville, Kentucky Wichita, Kansas San Francisco, California	Athens, Greece
36° N	Raleigh, North Carolina Las Vegas, Nevada	Tokyo, Japan
34° N	Columbia, South Carolina Los Angeles, California	Fez, Morocco
33° N	Dallas, Texas	
30° N	New Orleans, Louisiana	Cairo, Egypt
29° N	San Antonio, Texas	New Delhi, India
26° N	Miami, Florida	
22° N		Hong Kong, China
21° N	Honolulu, Hawaii	
19° N	Mexico City, Mexico	Mumbai (Bombay), India
15° N	Guatemala City, Guatemala	Manila, Philippines
10° N	Caracas, Venezuela	
4° N	Bogota, Columbia	
1° N		Singapore
12° S	Lima, Peru	
23° S	Rio de Janeiro, Brazil	
26° S		Johannesburg, South Africa
34° S		Sydney, Australia Cape Town, South Africa
35° S	Buenos Aires, Argentina	
37° S		Auckland, New Zealand
38° S		Melbourne, Australia
41° S		Wellington, New Zealand

Appendix A. Search Strategy for Primary Studies

a. Efficacy Search in Medline®

Database: Ovid MEDLINE®, CCTR (1969 to April 2009)

1. exp Vitamin D/
2. (25-hydroxy vit D or plasma vit D or 25OHD or 25-OHD).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. (25OHD3 or “25(OH)D3” or 25-OHD3 or “25-(OH)D3”).tw.
4. (“25(OH)D” or “25-(OH)D” or “25-OH-D”).tw.
5. 25-hydroxycholecalciferol.tw.
6. 25-hydroxyergocalciferol.tw.
7. calcidiol.tw.
8. Calcifediol/
9. (vit adj (d or d2 or d3)).mp.
10. Ergocalciferols/
11. Ergocalciferol$.tw.
12. Cholecalciferol/
13. Cholecalciferol$.tw.
14. calciferol.tw.
15. or/1-14
16. exp Calcium/
17. exp Calcium Carbonate/ or exp Calcium Citrate/ or exp Calcium Phosphates/ or exp Calcium Malate/
18. exp Calcium, Dietary/
19. calcium.tw.
20. or/16-19
21. (ANIMALS not HUMAN).sh.
22. *Dialysis/ or *hemodialysis/ or *peritoneal dialysis/
23. 15 or 20
24. 23 not 21
25. 24 not 22
26. limit 25 to (addresses or bibliography or biography or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news or newspaper article or “review”)
27. 25 not 26
28. limit 27 to english language
29. randomized controlled trial.pt.
30. controlled clinical trial.pt.
31. randomized controlled trials/
32. Random Allocation/
33. Double-blind Method/
34. Single-Blind Method/
35. clinical trial.pt.

36. Clinical Trials.mp. or exp Clinical Trials/
37. (clinic$ adj25 trial$).tw.
38. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
39. Placebos/
40. placebo$.tw.
41. random$.tw.
42. trial$.tw.
43. (latin adj square).tw.
44. Comparative Study.tw.
45. exp Evaluation studies/
46. Follow-Up Studies/
47. Prospective Studies/
48. (control$ or prospectiv$ or volunteer$).tw.
49. Cross-Over Studies/
50. or/29-49
51. 50 and 28
52. 28 not 51
53. limit 51 to yr="1969-2008"
54. limit 52 to yr="1969-2008"
55. 53 not ("200810$" or "200811$" or "200812$").ed.
56. 54 not ("200810$" or "200811$" or "200812$").ed.
57. 55 or 56
58. exp Vitamin D/
59. (25-hydroxy vit D or plasma vit D or 25OHD or 25-OHD).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
60. (25OHD3 or "25(OH)D3" or 25-OHD3 or "25-(OH)D3").tw.
61. ("25(OH)D" or "25-(OH)D" or "25-OH-D").tw.
62. 25-hydroxycholecalciferol.tw.
63. 25-hydroxyergocalciferol.tw.
64. calcidiol.tw.
65. Calcifediol/
66. (vit adj (d or d2 or d3)).mp.
67. Ergocalciferols/
68. Ergocalciferol$.tw.
69. Cholecalciferol/
70. Cholecalciferol$.tw.
71. calciferol.tw.
72. or/58-71
73. exp Calcium/
74. exp Calcium Carbonate/ or exp Calcium Citrate/ or exp Calcium Phosphates/ or exp Calcium Malate/
75. exp Calcium, Dietary/
76. calcium.tw.
77. or/73-76
78. (ANIMALS not HUMAN).sh.
79. (ANIMALS not HUMAN).sh.

80. 72 or 77
81. 80 not 78
82. 81 not 79
83. limit 82 to (addresses or bibliography or biography or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news or newspaper article or “review”)
84. 82 not 83
85. limit 84 to english language
86. randomized controlled trial.pt.
87. controlled clinical trial.pt.
88. randomized controlled trials/
89. Random Allocation/
90. Double-blind Method/
91. Single-Blind Method/
92. clinical trial.pt.
93. Clinical Trials.mp. or exp Clinical Trials/
94. (clinic$ adj25 trial$).tw.
95. ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw.
96. Placebos/
97. placebo$.tw.
98. random$.tw.
99. trial$.tw.
100. (latin adj square).tw.
101. Comparative Study.tw.
102. exp Evaluation studies/
103. Follow-Up Studies/
104. Prospective Studies/
105. (control$ or prospectiv$ or volunteer$).tw.
106. Cross-Over Studies/
107. or/86-106
108. 107 and 85
109. 85 not 108
110. limit 108 to yr=“1969-2008”
111. limit 109 to yr=“1969-2008”
112. 110 not (“200810$” or “200811$” or “200812$”).ed.
113. 111 not (“200810$” or “200811$” or “200812$”).ed.
114. 112 or 113
115. verapamil.mp. or 52-53-9.rn.
116. nifedipine.mp. or 21829-25-4.rn.
117. diltiazem.mp. or 42399-41-7.rn.
118. Azelnidipine.mp. or 123524-52-7.rn.
119. nicardipine.mp. or 55985-32-5.rn.
120. felodipine.mp. or 72509-76-3.rn.
121. mepirodipine.mp. or 104713-75-9.rn.
122. Amlodipine.mp. or 88150-42-9.rn.

123. isradipine.mp. or 75695-93-1.rn.
124. bepridil.mp. or 64706-54-3.rn.
125. gallopamil.mp. or 16662-47-8.rn.
126. aranidipine.mp. or 86780-90-7.rn.
127. nitrendipine.mp. or 39562-70-4.rn.
128. Barnidipine.mp.
129. benidipine.mp. or 105979-17-7.rn.
130. Cilnidipine.mp. or 132203-70-4.rn.
131. clevidipine.mp.
132. efonidipine.mp. or 111011-53-1.rn.
133. Lacidipine.mp. or 103890-78-4.rn.
134. Lercanidipine.mp. or 100427-26-7.rn.
135. Manidipine.mp. or 89226-50-6.rn.
136. Nilvadipine.mp. or 75530-68-6.rn.
137. Nimodipine.mp. or 66085-59-4.rn.
138. Nisoldipine.mp. or 63675-72-9.rn.
139. Pranidipine.mp. or 99522-79-9.rn.
140. ((calcium or Ca) adj3 channel$).mp.
141. ((calcium or Ca) adj3 agonist$).mp.
142. (intracellular adj2 (calcium or Ca)).mp.
143. or/115-142
144. weight loss.mp. or exp Weight Loss/
145. body mass index.mp. or exp Body Mass Index/ or exp Body Mass/ or body mass.mp. or exp body weight/ or body weight.mp.
146. 144 or 145
147. obesity.mp. or exp OBESITY/pc, di, ep, et
148. or/144-147
149. limit 148 to (“all infant (birth to 23 months)” or “newborn infant (birth to 1 month)” or “infant (1 to 23 months)” or “preschool child (2 to 5 years)”)
150. limit 149 to (“all adult (19 plus years)” or “child (6 to 12 years)” or “adolescent (13 to 18 years)” or “adult (19 to 44 years)” or “middle age (45 to 64 years)” or “middle aged (45 plus years)” or “all aged (65 and over)” or “aged (80 and over)”)
151. 149 not 150
152. 148 not 151
153. exp Body Height/
154. exp body size/
155. growth velocity.af.
156. growth retardation.af.
157. growth delay.af.
158. growth restriction.af.
159. (height adj6 restrict$).af.
160. linear velocity.af.
161. (height adj6 delay).af.
162. length delay.af.
163. (length adj6 retardation).af.
164. or/153-163

165. limit 164 to (“all infant (birth to 23 months)” or “all child (0 to 18 years)” or “newborn infant (birth to 1 month)” or “infant (1 to 23 months)” or “preschool child (2 to 5 years)” or “child (6 to 12 years)” or “adolescent (13 to 18 years)”)
166. 164 not 165
167. limit 166 to (“all adult (19 plus years)” or “adult (19 to 44 years)” or “middle age (45 to 64 years)” or “middle aged (45 plus years)” or “all aged (65 and over)” or “aged (80 and over)”)
168. 164 not 167
169. Bone Density/
170. exp Osteoporosis/
171. ((bone$ or plate$) adj3 mineral$).tw.
172. (bone adj2 (loss or turnover or densi$)).tw.
173. (Skelet$ adj2 (mineral$ or development$)).tw.
174. mineralization defect$.tw.
175. Mineral$ content$.tw.
176. BMC.tw.
177. Osteoporo$.tw.
178. Osteomalac$.tw.
179. Osteopath$.tw.
180. Bone Development/
181. Osteogenesis/
182. fracture$.tw.
183. Accidental Falls/
184. falls.tw.
185. exp “Bone and Bones”/
186. or/169-185
187. Rickets/
188. rachitis.tw.
189. rickets.tw.
190. or/187-189
191. tooth loss.mp. or exp Tooth Loss/
192. 190 or 186 or 191
193. limit 192 to yr=“2006-2008”
194. exp Cardiovascular Diseases/pc, di, ep, et
195. Cardi$.mp.
196. 195
197. Coronary.mp.
198. heart disease$.mp.
199. Myocardial infarct$.mp.
200. exp Cerebrovascular Accident/
201. stroke.tw.
202. Transient Ischemic Attack.tw.
203. exp Ischemia/
204. cardioprotect$.mp.
205. Pulmonary Embol$.tw.
206. Heart failure$.tw.
207. (embol$ or thromb$).tw.

208. exp Peripheral Vascular Diseases/ or peripheral artery disease.mp.
209. arterial occlusive diseases/
210. or/194-209
211. limit 210 to “all adult (19 plus years)”
212. exp hypertension/pc, di, ep, et
213. exp hypertension, renal/
214. hypertens$.af.
215. high blood pressure.af.
216. (eleva$ adj2 blood pressure).tw.
217. systolic blood pressure/
218. diastolic blood pressure/
219. mean arterial pressure/
220. or/212-219
221. limit 220 to “all adult (19 plus years)”
222. exp Neoplasms/dh, pc, et, di, ep [Diet Therapy, Prevention & Control, Etiology, Diagnosis, Epidemiology]
223. (“cancer risk” or “melanoma risk” or “lymphoma risk” or “leukemia risk” or “myeloma risk” or “sarcoma risk”).tw.
224. ((“risk of” or “occurrence of”) and (cancer$ or neoplasm$ or malignan$ or adenocarcinom$ or carcinom$ or melanom$ or lymphom$ or leuk?emi$ or myelodysplas$ or myelom$ or sarcom$)).tw.
225. 222 or 224 or 223
226. colon polyps.mp. or exp adenomatous polyps/ or exp colonic polyps/
227. (colon$ or rectum or rectal or colorectum or colorectal).ti,ab.
228. (adenoma$ or polyps or polyp).ti,ab.
229. 228 and 227
230. 229 or 226
231. mammography.mp. or exp mammography/
232. mammog$.ti,ab.
233. 231 or 232
234. dens$.ti,ab.
235. 233 and 234
236. prostate specific antigen.mp. or exp prostate-specific antigen/
237. (aberrant crypt$ foc$ or ACF).ti,ab.
238. (prostat$ and (intraepitheli$ or intra-epitheli$ or intra epitheli$) and Neoplas$).ab,ti.
239. 236 or 238 or 235 or 237 or 230
240. type 1 diabetes mellitus.mp. or exp Diabetes Mellitus, Type 1/
241. psoriasis.mp. or exp Psoriasis/
242. rheumatoid arthritis.mp. or exp Arthritis, Rheumatoid/
243. multiple sclerosis.mp. or exp Multiple Sclerosis/
244. inflammatory bowel disease.mp. or exp Inflammatory Bowel Diseases/
245. ulcerative colitis.mp. or exp Colitis, Ulcerative/
246. Crohn’s disease.mp. or exp Crohn Disease/
247. 240 or 241 or 242 or 243 or 244 or 245 or 246
248. tuberculosis.mp. or exp Tuberculosis/
249. influenza.mp. or exp Influenza, Human/

250. 248 or 249
251. exp “Activities of Daily Living”/
252. muscle strength.mp. or exp Muscle Strength/
253. exp Musculoskeletal Equilibrium/ or exp Walking/
254. (“balance test” or “timed walk” or “physical performance” or “hand-grip strength”).tw.
255. exp Hand Strength/
256. exp Muscles/
257. (“walking time” or “muscle strength”).tw.
258. or/251-257
259. limit 258 to (“all adult (19 plus years)” or “all aged (65 and over)” or “aged (80 and over)”)
260. exp Pre-eclampsia/
261. (pre-eclampsia or preeclampsia).mp.
262. pregnancy complication$.mp. or exp Pregnancy Complications/
263. or/260-262
264. limit 263 to male
265. limit 263 to female
266. 264 not 265
267. 263 not 266
268. limit 267 to animal
269. limit 267 to human
270. 268 not 269
271. 267 not 270
272. limit 271 to english language
273. exp infant,low birth weight/
274. low birth weight.af.
275. exp infant, premature/
276. (“small for gestational age” or sga).af.
277. ((preterm or prematur$) adj6 (infant or newborn)).af.
278. or/273-277
279. exp Milk, Human/
280. human milk.mp.
281. (human adj2 milk).tw.
282. breast milk.mp.
283. breastmilk.mp.
284. breast feeding.mp.
285. breastfeed$.mp.
286. breast fed.mp.
287. breastfed.mp.
288. (breast adj2 fed).tw.
289. exp lactation/
290. (lactating or lactation).mp.
291. or/279-290
292. Mortality.mp. or exp Mortality/
293. Fatal Outcome.mp. or exp Fatal Outcome/
294. exp Death/ or exp “Cause of Death”/ or death.mp.
295. Survival Rate.mp. or exp Survival Rate/

296. 295 or 292 or 294 or 293
297. heterotopic ossification.mp. or exp Ossification, Heterotopic/
298. myositis ossificans.mp. or exp Myositis Ossificans/
299. calcinosis.mp. or exp Calcinosis/
300. extraosseous calcification.mp.
301. metaplastic calcification.mp.
302. myo-osteosis.mp.
303. neurogenic osteoma.mp.
304. osseous heteroplasia.mp.
305. ossifying fibromyopathy.mp.
306. para-articular calcification.mp.
307. heterotopic calcification.mp.
308. pathological bone.mp.
309. pathological calcification.mp.
310. periarticular calcification.mp.
311. synostosis.mp.
312. ectopic bone.mp.
313. heterotopic bone.mp.
314. dystrophic ossification.mp.
315. ectopic ossification.mp.
316. metaplastic ossification.mp.
317. para-articular ossification.mp.
318. periarticular ossification.mp.
319. pathological ossification.mp.
320. ectopic calcification.mp.
321. soft tissue calcification.mp.
322. (vascular adj3 calcification).mp.
323. (aort$ adj3 calcification).mp.
324. (valv$ adj3 calcification).mp.
325. or/297-324
326. limit 325 to animal
327. limit 325 to human
328. 326 not 327
329. 325 not 328
330. limit 329 to english language
331. exp kidney disease/
332. exp kidney/
333. kidney.mp.
334. renal.af.
335. nephro$.af.
336. exp renal replacement therapy/
337. exp kidney, artificial/
338. (hemodialy$ or haemodialy$ or dialy$).af.
339. exp Kidney Glomerulus/
340. exp Kidney Function Tests/
341. ur?emia.tw.

342. exp Kidney Calculi/
343. (kidney stone$ or renal stone$ or renal calcul$ or kidney calcul$ or nephrolith$).af.
344. 343 not 342
345. exp nephrolithiasis/
346. or/331-345
347. allerg$.mp. or exp Hypersensitivity/

b. Overall Search Strategy for Outcomes of Upper Limits

Database: Ovid MEDLINE®, CCTR (from 1966 to December 2008)

1. exp Vitamin D/
2. (25-hydroxy vit D or plasma vit D or 25OHD or 25-OHD).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. (25OHD3 or “25(OH)D3” or 25-OHD3 or “25-(OH)D3”).tw.
4. (“25(OH)D” or “25-(OH)D” or “25-OH-D”).tw.
5. 25-hydroxycholecalciferol.tw.
6. 25-hydroxyergocalciferol.tw.
7. calcidiol.tw.
8. Calcifediol/
9. (vit adj (d or d2 or d3)).mp.
10. Ergocalciferols/
11. Ergocalciferol$.tw.
12. Cholecalciferol/
13. Cholecalciferol$.tw.
14. calciferol.tw.
15. exp Calcium Carbonate/ or exp Calcium Citrate/ or exp Calcium Phosphates/ or exp Calcium Malate/
16. or/1-15
17. supplement$.tw.
18. exp Dietary Supplements/to, ae, po, ut [Toxicity, Adverse Effects, Poisoning, Utilization]
19. No-Observed-Adverse-Effect Level/
20. upper limit$.tw.
21. UL.tw.
22. (excess$ or toxic$).tw.
23. vit d intox$.tw.
24. (noael or noel).tw.
25. (no observed adj2 effect$).tw.
26. or/17-25
27. 26 and 16
28. (ANIMALS not HUMAN).sh.
29. *Dialysis/ or *hemodialysis/ or *peritoneal dialysis/
30. 27 not 28
31. 30 not 29
32. limit 31 to (addresses or bibliography or biography or comment or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news or “review”)
33. 31 not 32

34. limit 33 to english language
35. exp kidney disease/
36. exp kidney, artificial/
37. exp Kidney Function Tests/
38. ur?emia.tw.
39. (kidney stone$ or renal stone$ or renal calcul$ or kidney calcul$ or nephrolith$).af.
40. exp nephrolithiasis/
41. heterotopic ossification.mp. or exp Ossification, Heterotopic/
42. myositis ossificans.mp. or exp Myositis Ossificans/
43. calcinosis.mp. or exp Calcinosis/
44. extraosseous calcification.mp.
45. metaplastic calcification.mp.
46. myo-osteosis.mp.
47. neurogenic osteoma.mp.
48. osseous heteroplasia.mp.
49. ossifying fibromyopathy.mp.
50. para-articular calcification.mp.
51. heterotopic calcification.mp.
52. pathological bone.mp.
53. pathological calcification.mp.
54. periarticular calcification.mp.
55. synostosis.mp.
56. ectopic bone.mp.
57. heterotopic bone.mp.
58. dystrophic ossification.mp.
59. ectopic ossification.mp.
60. metaplastic ossification.mp.
61. para-articular ossification.mp.
62. periarticular ossification.mp.
63. pathological ossification.mp.
64. ectopic calcification.mp.
65. soft tissue calcification.mp.
66. (vascular adj3 calcification).mp.
67. (aort$ adj3 calcification).mp.
68. (valv$ adj3 calcification).mp.
69. or/41-68
70. Calcification, Physiologic/de [Drug Effects]
71. Hypercalcemia/
72. Kidney Calculi/
73. Nephrocalcinosis/
74. Urinary Calculi/
75. Bladder Calculi/
76. Ureteral Calculi/
77. Calcinosis/
78. Hypercalcemi$.tw.
79. (Burnett$ adj2 syndrome$).tw.

80. Hypercalciuri$.tw.
81. or/70-80
82. psoriasis.mp. or exp Psoriasis/
83. 81 or 69 or 82
84. 34 and 83
85. limit 84 to case reports
86. 84 not 85

2013 UPDATE SEARCH METHODOLOGIES

EFFICACY SEARCH IN MEDLINE®

DATABASE SEARCHED & TIME PERIOD COVERED:
Medline® on OVID – 1/1/2013-12/30/2013

LANGUAGE:
English

SEARCH STRATEGY:
exp Vitamin D/ or (25-hydroxy vit$ D or plasma vit$ D or 25OHD or 25-OHD).mp. or (25OHD3 or "25(OH)D3" or 25-OHD3 or "25-(OH)D3").tw. or ("25(OH)D" or "25-(OH)D" or "25-OH-D").tw. or 25-hydroxycholecalciferol.tw. or 25-hydroxyergocalciferol.tw. or calcidiol.tw. or Calcifediol/ or (vit$ adj (d or d2 or d3)).mp. or Ergocalciferols/ or Ergocalciferol$.tw. or Cholecalciferol/ or Cholecalciferol$.tw. or calciferol.tw.
AND
(randomized controlled trial or controlled clinical trial).pt. or randomized controlled trials/ or Random Allocation/ or Double-blind Method/ or Single-Blind Method/ or clinical trial.pt. or Clinical Trials.mp. or exp Clinical Trials/ or (clinic$ adj25 trial$).tw. or ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$)).tw. or Placebos/ or placebo$.tw. or random$.tw. or trial$.tw. or (latin adj square).tw. or Comparative Study.tw. or exp Evaluation studies/ or Follow-Up Studies/ or Prospective Studies/ or (control$ or prospectiv$ or volunteer$).tw. or Cross-Over Studies/
NOT
addresses or autobiography or bibliography or biography or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news or newspaper article
NOT
(animals not human).sh.

SEARCH #2 - UPPER LIMIT:
DATABASE SEARCHED & TIME PERIOD COVERED:
Medline® on OVID – 1/1/2013-12/30/2013

LANGUAGE:
English

SEARCH STRATEGY:
exp Vitamin D/ or (25-hydroxy vit$ D or plasma vit$ D or 25OHD or 25-OHD).mp. or (25OHD3 or "25(OH)D3" or 25-OHD3 or "25-(OH)D3").tw. or ("25(OH)D" or "25-(OH)D" or "25-OH-D").tw. or 25-hydroxycholecalciferol.tw. or 25-hydroxyergocalciferol.tw. or calcidiol.tw. or Calcifediol/ or (vit$ adj (d or d2 or d3)).mp. or Ergocalciferols/ or Ergocalciferol$.tw. or Cholecalciferol/ or Cholecalciferol$.tw. or calciferol.tw.
AND

supplement$.tw. or exp Dietary Supplements/to, ae, po, ut or No-Observed-Adverse-Effect Level/ or upper limit$.tw. or UL.tw. or (excess$ or toxic$).tw. or vit$ d intox$.tw. or (noael or noel).tw. or (no observed adj2 effect$).tw.
AND
heterotopic ossification.mp. or exp Ossification, Heterotopic/ or myositis ossificans.mp. or exp Myositis Ossificans/ or calcinosis.mp. or exp Calcinosis/ or extraosseous calcification.mp. or metaplastic calcification.mp. or myo-osteosis.mp. or neurogenic osteoma.mp. or osseous heteroplasia.mp. or ossifying fibromyopathy.mp. or para-articular calcification.mp. or heterotopic calcification.mp. or synostosis.mp. or ectopic bone.mp. or heterotopic bone.mp. or dystrophic ossification.mp. or ectopic ossification.mp. or metaplastic ossification.mp. or para-articular ossification.mp. or soft tissue calcification.mp. or (vascular adj3 calcification).mp. or (aort$ adj3 calcification).mp. or (valv$ adj3 calcification).mp. or (pathological bone or pathological calcification or periarticular calcification).mp. or (periarticular ossification or pathological ossification or ectopic calcification).mp. or Calcification, Physiologic/de or Hypercalcemia/ or Kidney Calculi/ or Nephrocalcinosis/ or Urinary Calculi/ or Bladder Calculi/ or Ureteral Calculi/ or Calcinosis/ or Hypercalcemi$.tw. or (Burnett$ adj2 syndrome$).tw. or Hypercalciuri$.tw. or psoriasis.mp. or exp Psoriasis/
NOT
*Dialysis/ or *hemodialysis/ or *peritoneal dialysis/
NOT
addresses or bibliography or biography or case reports or comment or dictionary or directory or duplicate publication or editorial or in vitro or interview or lectures or letter or news

SEARCH #3:

DATABASE SEARCHED & TIME PERIOD COVERED:
COCHRANE TRIALS, SYSTEMATIC REVIEWS, AND OTHER REVIEWS DATABASES 1/1/2013-12/31/2013

LANGUAGE:
English

SEARCH STRATEGY:
‘“Vitamin D” or 25-hydroxy vit* D or “25-hydroxyvitamin d” OR plasma vit* D or 25OHD or 25-OHD or 25OHD3 or “25(OH)D3” or 25-OHD3 or “25-(OH)D3” or “25(OH)D” or “25-(OH)D” or “25-OH-D” OR 25-hydroxycholecalciferol or 25-hydroxyergocalciferol or calcidiol or (vit* adj (d or d2 or d3)) or Ergocalciferol* or Cholecalciferol* or calciferol* in Title, Abstract, Keywords

Appendix B. Search Strategy for Systematic Reviews

Databases: MEDLINE®, the Cochrane Database of Systemic Reviews, and the Health Technology Assessments (up to December 2008)

1. (meta-analys$ or metaanalys$).mp. [mp=title, abstract, full text, keywords, caption text]
2. (systematic review$ or systematic literature or evidence-based or evidence review$).mp. [mp=title, abstract, full text, keywords, caption text]
3. (EBM or EBR or EBRs).mp. [mp=title, abstract, full text, keywords, caption text]
4. or/1-3
5. (vitamin D or cholecalciferol or ergocalciferol or hydroxy vitamin D or calcitriol).mp. [mp=title, abstract, full text, keywords, caption text]
6. Calcium.mp. [mp=title, abstract, full text, keywords, caption text]
7. 5 or 6
8. 4 and 7

Appendix C. Evidence Tables for the Current Report

List of Abbreviations and Acronyms Included in Evidence Tables

Abbreviation	Term
ACS	Aortic calcification score
ADL	Activities of Daily Living
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BP	Blood pressure
CHS	Cardiovascular Health Study
CKD	Chronic kidney disease
CRC	Colorectal cancer
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
EPIC	European Prospective Investigation into Cancer and Nutrition
ESTHER	EStrogen and THromboEmbolism Risk Study
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
HLA	Human leukocyte antigen
HPFS	Health Professionals Follow-Up Study
HR	Hazard ratio
InChianti	Invecchiare nel Chianti
INTAPP	International Trial of Antioxidants in the Prevention of Pre-eclampsia
InChianti	Invecchiare nel Chianti
KORA	Cooperative Health Research in the Region Augsburg
InChianti	Invecchiare nel Chianti

Abbreviation	Term
LDL	Low-density lipoprotein
MEC	Mobile Examination Center
MESA	Multi-ethnic Study of Atherosclerosis
MI	Myocardial infarction
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease Study
MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease Study
NSAIDS	Non-steroidal anti-inflammatories
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
PASE	Physical Activity Score For The Elderly
PTH	Parathyroid hormone
Q	Quartile
RR	Relative risk
SC	Size-corrected
SD	Standard deviation
SBP	Systolic blood pressure
SES	Socioeconomic status
SPPB	Secondary-Short Physical Performance Battery
TUAG	Timed Up and Go
VTE	Venous thromboembolism
YRS	Years

Vitamin D Update Evidence Table

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Afzal et al., 2013	Prospective Cohort	19–50 years; 51–70 years; free of cancer; 20–100 years of age	Not specified		hospital	Denmark	9791/9791/55	58/47–65		Not Reported	

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Afzal et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Education; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Tobacco Consumption In Pack-Years, Alcohol Consumption In Grams Per Week, Level Of Leisure Time, Work-Related Physical Activity; Other - Competing Risk Of Death	Primary-All Cancer	25(OH)D	50% reduction in plasma levels	28 yrs	2488/9791	adjusted/HR	1.06	1.02, 1.11	
				Primary-Pancreatic Cancer	25(OH)D	50% reduction in plasma levels	28 yrs	109/9791	adjusted/HR	1.05	0.84, 1.30	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Afzal et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Almquist et al., 2010	Nested Case Control	19–50 years; 51–70 years; women	Not specified	Malmo¨ Diet and Cancer Study	Private Foundation	Malmo, Sweden	1528/745/100	57 (7.2)/NR		Post menopausal; Other; pre- and peri-menopausal	quartile of mean 25OHD2: 16.2, 20.0, 22.7, 26.2 quartile of mean 25OHD3: 45.2, 62.0, 73.7, 93.4 quartile of total 25OHD: 57.5, 80.3, 96.3, 126.1

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Almquist et al., 2010	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)-Age, SES; Anthropometrics-BMI; Medical Conditions-Menopausal Status; Sun Exposure-Screening Season; Smoking, Other Lifestyle Factors-Smoking Status, Alcohol Consumption	Primary-Breast Cancer	25(0H)D3	Quartile 1(<=70nmol/l)	7.0 years	NR/213	adjusted/OR	1	reference	
					25(0H)D3	Quartile 2 (71–86nmol/L)	7.0 years	NR/164	adjusted/OR	0.84	0.60, 1.15	
					25(0H)D3	Quartile 3(87–105nmol/L)	7.0 years	NR/176	adjusted/OR	0.84	0.60, 1.17	
					25(0H)D3	Quartile 4(>=106nmol/L)	7.0 years	NR/192	adjusted/OR	0.93	0.66, 1.33	0.710
					25(0H)D2+D3	Quartile 1(<=71nmol/l)	7.0 years	NR/191	adjusted/OR	1	reference	
					25(0H)D2+D3	Quartile 2 (72–87nmol/L)	7.0 years	NR/170	adjusted/OR	0.95	0.68, 1.31	
					25(0H)D2+D3	Quartile 3(88–106nmol/L)	7.0 years	NR/183	adjusted/OR	0.94	0.68, 1.32	
					25(0H)D2+D3	Quartile 4(>=107nmol/L)	7.0 years	NR/191	adjusted/OR	0.96	0.68, 1.37	0.780

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Almquist et al., 2010	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	**Justification of Final Adjusted Model Selection?**	**Clear Definition of Outcome Including Time of Ascertainment?**	**Loss to Followup <20%?**	**Do the Authors Specify a Primary Outcome?**	**Prospective Collection of Data?**	**Analysis Was Planned When Cohort Was Formed?**	**Justification of Sample Size (Includes Sample Size Calculations)?**	**Overall Grade**	**Explanation for Grade (if Not A)**
Y	Y	Y	Y	NA	Y	N	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Anderson et al., 2010	Prospective Cohort	The presence of at least one Vit D measurement from 2000 to 2009 in the electronic medical record	Not specified		Private Foundation	USA; Murray UT	41,504/ 41504/ 74.8	55 (21)/NR		Not Reported	

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR, RR, HR, %)**	**Result**	**95% CI**	**P-val**
Anderson et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/ Ethnicity)—Age, Gender; Medical Conditions—Type 2 Diabetes, Hyperlipidemia, Hypertension, Peripheral Vascular Disease	Secondary-Hypertension	serum 25(OH)D	very low (Vit D level <= 15 ng/ml)	1.3 yrs on average	7848/ 15121	adjusted/HR	1.62	1.38, 1.89	P < 0.0001
					serum 25(OH)D	low (Vit D level 16–30 ng/ml)	1.3 yrs on average	8530/ 19474	adjusted/HR	1.18	1.05, 1.33	P = 0.005
					serum 25(OH)D	normal (Vit D level > 30 ng/ml)	1.3 yrs on average	2750/ 6909	adjusted/HR	1	reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Anderson et al., 2010	N	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	**Justification of Final Adjusted Model Selection?**	**Clear Definition of Outcome Including Time of Ascertainment?**	**Loss to Followup <20%?**	**Do the Authors Specify a Primary Outcome?**	**Prospective Collection of Data?**	**Analysis Was Planned When Cohort Was Formed?**	**Justification of Sample Size (Includes Sample Size Calculations)?**	**Overall Grade**	**Explanation for Grade (if Not A)**
Y	N	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Aregbesola et al., 2013	Prospective Cohort	51–70 years; age 53–73 years	Current cancer; pneumonia, lung tuberculosis, bronchial asthma, chronic bronchitis	Kuopio Ischemic Heart Disease Risk Factor (KIHD) study	Government	Finland; Kuopio	1421/ 1421/ 49.1	62.5 (6.5)/ NR		Not Reported	mean serum 25(OH)D3: 43.5 nmol/l (SD: 17.8)

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow -up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Aregbesola et al., 2013	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Multivitamin Use; Demographics (Age, Sex, Race/Ethnicity)- Age, Gender; Anthropometrics- Body Mass Index; Sun Exposure- High Sun Exposure At Baseline Sampling; Smoking, Other Lifestyle Factors- Smoking, Leisure Time Physical Activity; Other - Year Of Education And Income, Occupation	Primary- Pneumonia	25(OH)D3	Tertile 1: 8.9–33.8	9.8 yrs	38/925	adjusted/HR	2.4	1.2, 4.9	0.021
					25(OH)D3	Tertile 2: 33.9–50.7	9.8 yrs	22/426	adjusted/HR	1.4	0.7, 2.8	
					25(OH)D3	Tertile 3: 50.8–112.8	9.8 yrs	13/70	adjusted/HR	1	reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Aregbesola et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	**Justification of Final Adjusted Model Selection?**	**Clear Definition of Outcome Including Time of Ascertainment?**	**Loss to Followup <20%?**	**Do the Authors Specify a Primary Outcome?**	**Prospective Collection of Data?**	**Analysis Was Planned When Cohort Was Formed?**	**Justification of Sample Size (Includes Sample Size Calculations)?**	**Overall Grade**	**Explanation for Grade (if Not A)**
Y	N	Y	Y	NA	Y	N	N	B	reference 9: http://rd.springer.com/article/10.1007/s00394-010-0138-3#page-1

Eligibility Criteria and Baseline Characteristics											
Author ,Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Baker et al., 2010	Nested Case Control	Pregnant or lactating women; singleton pregnancies; absence of chronic medical illnesses	any preexisting chronic medical condition; pregestational hypertension, kidney disease, diabetes, thrombophilias; congenital fetal anomalies; multiple gestation		Private Foundation	USA; Chapel Hill, North Carolina	255/241/100	28/NR	Non-Hispanic White=71; Hispanic=62; Non-Hispanic Black=96; Race_other1=12	Other; pregnant	controls: median 25(OH)D 98 nmol/l (IQR 68–113) cases: median 25(OH)D 75 nmol/l (IQR 47–107)

Main Analyses												
Author ,Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow -up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Baker et al., 2010	Nested Case Control	race/ethnicity	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Sun Exposure- Season Of Blood Draw; Other - Gestational Age At Serum Collection	Primary-Severe Preeclampsia	25(OH)D	< 50	NR	22/160	adjusted/OR	5.41	2.02, 14.52	0.001
					25(OH)D	50–74.9	NR	10/51	adjusted/OR	2.16	0.85, 5.40	0.1
					25(OH)D	>=75	NR	11/30	adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Baker et al., 2010	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	**Justification of Final Adjusted Model Selection?**	**Clear Definition of Outcome Including Time of Ascertainment?**	**Loss to Followup <20%?**	**Do the Authors Specify a Primary Outcome?**	**Prospective Collection of Data?**	**Analysis Was Planned When Cohort Was Formed?**	**Justification of Sample Size (Includes Sample Size Calculations)?**	**Overall Grade**	**Explanation for Grade (if Not A)**
Y	N	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Baker et al., 2011	Nested Case Control	Pregnant or lactating women	Type 2 DM; preeclampsia, gestational hypertension; medically indicated preterm delivery; multiple gestation; major congenital fetal anomalies; kidney disease; thrombophilias; other major chronic disease		Hospital	USA; Chapel Hill, NC	160/160/100	33/30–37	Non-Hispanic White=53; Hispanic=11; Non-Hispanic Black=33; Race_other1=5	NR	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Baker et al., 2011	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Sun Exposure- Season Of Blood Draw; Other - Gestational Age At Serum Collection	Primary-Preterm Birth	25(OH)D	<50 nmol/L	NR	3/11	adjusted/OR	0.82	0.19, 3.57	
					25(OH)D	50–74.9 nmol/L	NR	8/32	adjusted/OR	0.87	0.34, 2.25	
					25(OH)D	>=75 nmol/L	NR	29/117	adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Baker et al., 2011	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	N	Y	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Barbour et al., 2012	Prospective Cohort	51–70 years; 70–79 years of age	difficulty with ADLs; cognitive impairment; inability to communicate with interviewer; intention to move; participation in other trial	Health ABC	Government	USA; Pittsburgh, PA and Memphis, TN	2640/2501/61 in lowest quartile	74.7 (2.9)/NR	Non-Hispanic Black=699	Not Reported	Dietary calcium intake, median (IQR) (mg/d) 717 (515–973) 736 (532–995) 719 (517–978) 716 (501–940) Supplemental calcium intake (% yes) 18.3 25.0 17.4 28.7 Supplemental vitamin D intake (% yes) 8.3 13.1 8.1 12.2 in order of groups: hip fracture no/yes,

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Barbour et al., 2012	Prospective Cohort	N/R	Other Nutrients Or Dietary Factors- Serum Calcium; Anthropometrics- Estimated BMD; Medical Conditions- Estimated GFR, Il-6; Other - Time To Complete 5 Chair Stands	Primary-Hip Fracture	25(OH)D	Quartile 1: =17.78 ng/ml	2 yrs	84/2501	adjusted/HR	1.92	0.97, 3.83	0.217
					25(OH)D	Quartile 2: 17.79–24.36 ng/ml	2 yrs		adjusted/HR	0.75	0.32, 1.72	
					25(OH)D	Quartile 3: 24.37–31.94 ng/ml	2 yrs		adjusted/HR	1.86	1.00, 3.45	
					25(OH)D	Quartile 4: >31.94 ng/ml	2 yrs		adjusted/HR	1	Reference	
				Primary-Nonspine Fracture	25(OH)D	Quartile 1: =17.78 ng/ml	2 yrs	247/2494	adjusted/HR	1.21	0.83, 1.75	0.752
					25(OH)D	Quartile 2: 17.79–24.36 ng/ml	2 yrs		adjusted/HR	1.01	0.68, 1.49	
					25(OH)D	Quartile 3: 24.37–31.94 ng/ml	2 yrs		adjusted/HR	1.12	0.78, 1.60	
					25(OH)D	Quartile 4: >31.94 ng/ml	2 yrs		adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Barbour et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	N	Y	B	post hoc power calculation Population a) sampling random Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Barnett et al., 2010	Nested Case Control	51–70 years; men; age =65 years	inability to walk without assistance from another person,; bilateral hip replacements; inability to provide self-reported data; residence not near a study site; judged by an investigator to have a medical condition that would result in imminent death; inability to understand and sign informed consent	Osteoporotic Fractures in Men (MrOS) study	Unclear	USA; Birmingham, Alabama; Palo Alto, California; San Diego, California; Minneapolis, Minnesota; Portland, Oregon; Pittsburgh, Pennsylvania	1648/1648/0	73.6 (5.9)/NR	Non-Hispanic White=901; Hispanic=28; Non-Hispanic Black=31; Asian=27; Race_other1= 13	Not Reported	25.1 ± 8.1 ng/ml in controls 25.5 ± 7.5 ng/ml in cases

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Barnett et al., 2010	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Race; Medical Conditions- Statin Use, NSAIDs Use; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Physical Activity Score For The Elderly (PASE) Score; Other - First Degree Relative With A History Of Prostate Cancer	Primary-Prostate Cancer	25(0H)D	Quartile 1(3.1–19.9ng/mL)	NR	68/411	adjusted/HR	1	reference	0.940
					25(0H)D	Quartile 2(20.0–24.9ng/mL)	NR	91/415	adjusted/HR	1.35	0.91, 2.01	
					25(0H)D	Quartile 3(25.0–29.9ng/mL)	NR	53/406	adjusted/HR	0.64	0.41, 1.00	
					25(0H)D	Quartile 4(30–75.6ng/mL)	NR	85/416	adjusted/HR	1.2	0.81, 1.78	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Barnett et al., 2010	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Belderbos et al., 2011	Prospective Cohort	0–6 months; Healthy; >=37 weeks GA	Not specified		Private Foundation	Utrecht, Netherland	161/NR/44	40 weeks (GA) (0.13)/NR	Race_other1= 70; Race_other2= 30		NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Belderbos et al., 2011	Prospective Cohort	NR	Anthropometrics- Birth Weight	Primary-Respiratory Syncytial Virus Bronchiolitis	25(0H)D	<50nmol/L-NR	NR	36/NR	Adjusted/RR	6.2	1.6, 24.9	
					25(0H)D	50–74nmol/L-NR	NR	48/NR	Adjusted/RR	1.3	NR	
					25(0H)D	>=75nmol/l-NR	NR	72/NR	Adjusted/RR	1	reference	0.13

Quality of Cohort or Nested Case-Control Studies										
Author,Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Belderbos et al., 2011	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author,Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Bodnar et al., 2010	Nested Case Control	Pregnant or lactating women; nulliparous, had no preexisting medical conditions, and delivered a live-born infant; had a maternal blood sample at <22 wk; self-identified as black or white	serum 25(OH)D concentrations were outside the detectable range		Government	USA; Pittsburgh, PA (latitude 40 degree N)	412/412/100	21/14–42	Non-Hispanic White=66; Non-Hispanic Black=34		NR

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Bodnar et al., 2010	Nested Case Control	none	Demographics (Age, Sex, Race/Ethnicity)- SES; Anthropometrics- Prepregnancy BMI,; Smoking, Other Lifestyle Factors- Smoking During Pregnancy	Primary-Small-For-Gestational Age Births	25(OH)D	<37.5 nmol/L-white women	NR	8/11	adjusted/OR	7.5	1.8, 31.9	
					25(OH)D	37.5–75 nmol/L-white women	NR	27/134	adjusted/OR	1	Reference	
					25(OH)D	>75 nmol/L-white women	NR	42/128	adjusted/OR	2.1	1.2, 3.8	
					25(OH)D	<37.5 nmol/L-black women	NR	17/65	adjusted/OR	1.5	0.6, 3.5	
					25(OH)D	37.5–75 nmol/L-black women	NR	13/63	adjusted/OR	1	Reference	
					25(OH)D	>75 nmol/L-black women	NR	4/11	adjusted/OR	2.2	0.5, 9.0	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Bodnar et al., 2010	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Bodnar et al., 2013	Prospective Cohort	Pregnant or lactating women; women carrying twin pregnancies; 16 weeks–20 weeks 3 days gestation	Not specified		Government	USA	211/211/100	NR/NR	Non-Hispanic White=621; Non-Hispanic Black=238; Race_other1= 156		NR

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Bodnar et al., 2013	Prospective Cohort	Not applicable	Demographics (Age, Sex, Race/Ethnicity)- Race/Ethnicity, Education; Anthropometrics- Prepregnancy BMI; Sun Exposure- Season; Smoking, Other Lifestyle Factors- Smoking Status; Other - Parity, Marital Status, Gestational Age At Blood Sampling, 17-A(Oh)progesterone	Primary-Preterm Birth At Less Than 35 Wk	25(OH)D	< 75	24–28 weeks gestation	42/85	adjusted/OR	1	reference	
					25(OH)D	>=75	24–28 weeks gestation	33/126	adjusted/OR	0.4	0.2, 0.8	
					25(OH)D	per 1-SD increase	24–28 weeks gestation	75/211	adjusted/OR	0.5	0.3, 0.8	
					25(OH)D	Q1 (median 43.6)	24–28 weeks gestation	27/52	adjusted/OR	1	reference	
					25(OH)D	Q2 (median 72.7)	24–28 weeks gestation	24/53	adjusted/OR	1	0.4, 2.5	
					25(OH)D	Q3 (median 95.4)	24–28 weeks gestation	15/53	adjusted/OR	0.4	0.2, 1.1	
					25(OH)D	Q4 (median 116)	24–28 weeks gestation	9/53	adjusted/OR	0.2	0.1, 0.7	
				Primary-Preterm Birth At Less Than 32 Wk	25(OH)D	< 75	24–28 weeks gestation	16/85	adjusted/OR	1	reference	
					25(OH)D	>=75	24–28 weeks gestation	9/126	adjusted/OR	0.2	0.1, 0.6	
					25(OH)D	per 1-SD increase	24–28 weeks gestation	25/211	adjusted/OR	0.4	0.2, 0.8	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	Q1 (median 43.6)	24–28 weeks gestation	10/52	adjusted/OR	1	reference	
					25(OH)D	Q2 (median 72.7)	24–28 weeks gestation	7/53	adjusted/OR	0.5	0.1, 1.7	
					25(OH)D	Q3 (median 95.4)	24–28 weeks gestation	6/53	adjusted/OR	0.4	0.1, 1.5	
					25(OH)D	Q4 (median 116)	24–28 weeks gestation	2/53	adjusted/OR	0.1	0.02, 0.7	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Bodnar et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Boer et al., 2012	Prospective Cohort	51–70 years; 65 years or greater; not institutionalized; expected to remain in the area** for at least 3 years	wheelchair bound in the home; receiving hospice treatment; chemotherapy; radiation therapy	Cardiovascular Health Study	Government	USA; multiple	1621/1621/70	74.0 (4.6)/NR	Non-Hispanic White=100		serum vitamin D: 66.2+/- 25.8 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Boer et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking, Physical Activity	Primary-Death	25(OH)D	Normal level	11 yrs	539/1126	adjusted/HR	1	Reference	NR
					25(OH)D	Low level (season specific, ranges 43–61 nmol/L)	11 yrs	287/495	adjusted/HR	1.32	1.14, 1.53	
				Primary-Hip Fracture	25(OH)D	Normal level	11 yrs	118/1126	adjusted/HR	1	Reference	NR
					25(OH)D	Low level (season specific, ranges 43–61 nmol/L)	11 yrs	72/495	adjusted/HR	1.34	0.97, 1.84	
				Primary-Cancer	25(OH)D	Normal level	11 yrs	259/1126	adjusted/HR	1	Reference	NR
					25(OH)D	Low level (season specific, ranges 43–61 nmol/L)	11 yrs	111/495	adjusted/HR	1.13	0.90, 1.42	
				Primary-MI	25(OH)D	Normal level	11 yrs	154/1126	adjusted/HR	1	Reference	NR
					25(OH)D	Low level (season specific, ranges 43–61 nmol/L)	11 yrs	67/495	adjusted/HR	1.24	0.91–1.70	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Boer et al., 2012	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Bolland et al., 2010	Prospective Cohort	Postmenopausal women; Healthy; normal lumber spine BMD; not taking agents for osteoporosis (including hormone replacement therapy or vitamin D supplements at doses >1000 IU/d); 25(OH)D >=25 nmol/L	Not specified	ACTRN 012605000242628	Government	New Zealand	1471/1471/100	74 (4.2)/NR		Post menopausal	Mean seasonally adjusted 25(OH)D concentration-50.5(17.7)nmol/L; Unadjusted mean-50.9(19.1)nmol/L.

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Bolland et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- Body Weight; Medical Conditions- Systolic Blood Pressure, And History Of Ischemic Heart Disease, Stroke Or Transient Ischemic Attack, Dyslipidemia, And Diabetes; Smoking, Other Lifestyle Factors- Smoking Status; Other - Treatment Allocation (Calcium Or Placebo)	Secondary-Death	25(OH)D2; calcium	<50 nmol/L (also took calcium)	5 yrs	21/363	adjusted/HR	1.2	0.6, 2.5	0.57
					25(OH)D2; calcium	>=50 nmol/L (also took calcium)	5 yrs	13/369	adjusted/HR	1	Reference	
					25(OH)D2	<50 nmol/L (no calcium)	5 yrs	13/373	adjusted/HR	0.9	0.4, 2.0	0.82
					25(OH)D2	>=50 nmol/L (no calcium)	5 yrs	16/366	adjusted/HR	1	Reference	
				Primary-MI	25(OH)D	<50 nmol/L	5 yrs	31/736	Adjusted/HR	1.2	0.7, 2.2	0.52
					25(OH)D	>=50 nmol/L	5 yrs	21/735	Adjusted/HR	1	Reference	
				Primary-Stroke	25(OH)D	<50 nmol/L	5 yrs	37/736	Adjusted/HR	1.4	0.8,2.5	0.20
					25(OH)D	>=50 nmol/L	5 yrs	22/735	Adjusted/HR	1	Reference	
				Primary-MI, Stroke, Or Sudden Death	25(OH)D	<50 nmol/L	5 yrs	65/736	Adjusted/HR	1.2	0.8, 1.8	0.34
					25(OH)D	>=50 nmol/L	5 yrs	45/735	Adjusted/HR	1	Reference	
				Primary-Tia	25(OH)D	<50 nmol/L	5 yrs	24/736	Adjusted/HR	1.1	0.6, 2.0	0.76
					25(OH)D	>=50 nmol/L	5 yrs	21/735	Adjusted/HR	1	Reference	
				Primary-Congestive Heart Failure	25(OH)D	<50 nmol/L	5 yrs	12/736	Adjusted/HR	1	0.4, 2.4	0.97
					25(OH)D	>=50 nmol/L	5 yrs	10/735	Adjusted/HR	1	Reference	
				Primary-Death	25(OH)D	<50 nmol/L	5 yrs	34/736	Adjusted/HR	0.9	0.5, 1.6	0.73
					25(OH)D	>=50 nmol/L	5 yrs	29/735	Adjusted/HR	1	1.00	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Bolland et al., 2010	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	Y	A	Justification of model- Y overall grade unchanged Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Brandstedt et al., 2012	Nested Case Control	51–70 years; born in 1923–1945; living in Malmo, Sweden	Not specified		Private Foundation	Malmo, Sweden	1886/1842/0	61.7 (6.4)/NR		Not Reported	NR

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Brandstedt et al., 2012	Nested Case Control	age, time of blood donation	Demographics (Age, Sex, Race/Ethnicity)- Education Level; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Alcohol Consumption, Smoking	Primary-Prostate Cancer	25(0H)D	Quartile 1(<=68nmol/L)	NR	206/448	adjusted/OR	1	reference	
					25(0H)D	Quartile 2(69–84nmol/L)	NR	237/469	adjusted/OR	1.25	0.95, 1.65	
					25(0H)D	Quartile3(85–102nmol/L)	NR	245/471	adjusted/OR	1.37	1.03, 1.82	
					25(0H)D	Quartile 4(>=103nmol/L)	NR	230/454	adjusted/OR	1.34	0.99, 1.82	0.048

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Brandstedt et al., 2012	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	**Justification of Final Adjusted Model Selection?**	**Clear Definition of Outcome Including Time of Ascertainment?**	**Loss to Followup <20%?**	**Do the Authors Specify a Primary Outcome?**	**Prospective Collection of Data?**	**Analysis Was Planned When Cohort Was Formed?**	**Justification of Sample Size (Includes Sample Size Calculations)?**	**Overall Grade**	**Explanation for Grade (if Not A)**
Y	N	Y	Y	NA	Y	Y	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Brodin et al., 2013	Prospective Cohort	19–50 years; 51–70 years; age >24 years	previous history of VTE; not officially registered inhabitants of the municipality of Tromso at baseline; missing values of serum 25(OH)D	Tromso study	Unclear	Norway	6021/5905/63	62 (10)/NR		Not Reported	mean 25(OH)D: 58.1 +/- 19.8 nmol/l

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Brodin et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- Body Mass Index; Smoking, Other Lifestyle Factors- Smoking, Physical Activity	Primary-Total Venous Thromboembolism	25(OH)D	<=44	10.7 yrs	50/1474	adjusted/HR	1	Reference	0.89
					25(OH)D	45–56	10.7 yrs	58/1470	adjusted/HR	0.72	0.41, 1.30	
					25(OH)D	57–69	10.7 yrs	46/1481	adjusted/HR	0.93	0.55, 1.50	
					25(OH)D	>=70	10.7 yrs	47/1480	adjusted/HR	0.76	0.45, 1.28	
					25(OH)D	per 1 sd decrease in serum 25(OH)D	10.7 yrs	201/5905	adjusted/HR	1.02	0.91, 1.22	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Brodin et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Brunner et al., 2011	RCT/CCT	51–70 years; Postmenopausal women; age 50–79 years	current daily use of at least 600 IU of supplemental vitamin D (single supplement and multivitamin combined) or calcitriol; history of renal calculi or hypercalcemia; predicted survival of less than 3 yr; current use of oral corticosteroids	Women's Health Initiative (WHI)	Government	Not reported	36,282/36282/ 100	NR/50–79	Non-Hispanic White=833; Hispanic=40; Non-Hispanic Black=91; Asian=19; Race_other1= 04; Race_other2= 12	Not Reported	NR

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Brunner et al., 2011	RCT/CCT	NR	NR	Primary-Total Cancer	Vit D3; elemental calcium	1,000 mg elemental calcium + 400 IU of vitamin D3	7 yrs	1306/18176	adjusted/HR	0.98	0.90, 1.05	0.78
						placebo	7 yrs	1333/18106	adjusted/HR	1	Reference	
				Primary-Invasive Breast Cancer	Vit D3; elemental calcium	1,000 mg elemental calcium + 400 IU of vitamin D3	7 yrs	505/18176	adjusted/HR	0.96	0.85, 1.09	0.26
						placebo	7 yrs	523/18106	adjusted/HR	1	Reference	
				Primary-Invasive Colon Cancer	Vit D3; elemental calcium	1,000 mg elemental calcium + 400 IU of vitamin D3	7 yrs	117/18176	adjusted/HR	0.98	0.76, 1.27	0.72
						placebo	7 yrs	118/18106	adjusted/HR	1	Reference	
				Primary-Invasive Rectal Cancer	Vit D3; elemental calcium	1,000 mg elemental calcium + 400 IU of vitamin D3	7 yrs	41/18176	adjusted/HR	1.42	0.88, 2.28	0.16
						placebo	7 yrs	29/18106	adjusted/HR	1	Reference	
				Primary-Invasive Pancreatic Cancer	Vit D3; elemental calcium	1,000 mg elemental calcium + 400 IU of vitamin D3	7 yrs	32/18176	adjusted/HR	0.88	0.55, 1.41	0.46
						placebo	7 yrs	36/18106	adjusted/HR	1	Reference	
				Primary-Cancer Mortality	Vit D3; elemental calcium	1,000 mg elemental calcium + 400 IU of vitamin D3	7 yrs	315/18176	adjusted/HR	0.9	0.77, 1.05	0.25
						placebo	7 yrs	347/18106	adjusted/HR	1	Reference	

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Brunner et al., 2011	RCT/CCT	Y	Y	N	N	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Burgi et al., 2011	Nested Case Control	Navy female recruits	Not specified		Government	USA	1200/1200/100	19.5 (1.8)/NR	Non-Hispanic White=54; Non-Hispanic Black=12; Race_other1= 34	Not Reported	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Burgi et al., 2011	Nested Case Control	age, race/ethnicity, length of military service, date of blood draw	Sun Exposure- Latitude Of Home	Primary-Stress Fracture	25(OH)D	1.5–19.7 ng/ml	NR	600/1200	adjusted/OR	1	Reference	0.02
					25(OH)D	19.8–26.6 ng/ml	NR		adjusted/OR	0.77	0.54, 1.11	
					25(OH)D	26.7–32.8 ng/ml	NR		adjusted/OR	0.76	0.52, 1.10	
					25(OH)D	32.9–39.8 ng/ml	NR		adjusted/OR	0.61	0.42, 0.91	
					25(OH)D	39.9–112.5 ng/ml	NR		adjusted/OR	0.51	0.34, 0.78	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Burgi et al., 2011	N	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	**Justification of Final Adjusted Model Selection?**	**Clear Definition of Outcome Including Time of Ascertainment?**	**Loss to Followup <20%?**	**Do the Authors Specify a Primary Outcome?**	**Prospective Collection of Data?**	**Analysis Was Planned When Cohort Was Formed?**	**Justification of Sample Size (Includes Sample Size Calculations)?**	**Overall Grade**	**Explanation for Grade (if Not A)**
Y	N	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Burns et al., 2012	RCT/CCT	expeditioners; free of disease; no use of medication known to affect bone	severe vit D deficiency (<12.5 nmol/L); serum Vit D >100 nmol/L		Trans-Antarctic Association, Private foundation: the Austin Hospital Medical Research Foundation.	Australian Antarctic Division	110/102/17	41/24–65	Non-Hispanic White=94		Monthly- 55+/-14 nmol/L Bi-monthly- 60+/-15 nmol/L Single dose-63+/-12 nmol/L

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Burns et al., 2012	RCT/CCT	NR	NR	Secondary-Femoral Neck BMD	D3 monthly (Vit D3 50,000 IU/month)		36	0.86 (sd=0.14)	final=0.85 (sd=0.13)	-0.06 (-0.12, 0)	0.06
					D3 bimonthly (Vit D3 50,000 IU in alternate months)		35	0.82 (sd=0.10)	final=0.82 (sd=0.10)	-0.09 (-0.15, -0.03)	.
					D3 single does (one does of Vit D3 50,000 IU pre departure)		31	0.9 (sd=0.13)	final=0.91 (sd=0.13)		.
				Secondary-Lumbar Spine (L1-L4) BMD	D3 monthly (Vit D3 50,000 IU/month)		36	1 (sd=0.17)	final=0.98 (sd=0.16)	-0.09 (-0.17, -0.01)	0.03
					D3 bimonthly (Vit D3 50,000 IU in alternate months)		35	1 (sd=0.10)	final=1.00 (sd=0.09)	-0.07 (-0.14, -0.0)	0.05
					D3 single does (one does of Vit D3 50,000 IU pre departure)		31	1.08 (sd=0.17)	final=1.07 (sd=0.18)		.
				Secondary-Total Proximal Femur BMD	D3 monthly (Vit D3 50,000 IU/month)		36	1.02 (sd=0.13)	final=0.85 (sd=0.13)	-0.23 (-0.30, -0.16)	.
					D3 bimonthly (Vit D3 50,000 IU in alternate months)		35	1.01 (sd=0.08)	final=1.01 (sd=0.08)	-0.07 (-0.13, -0.01)	0.02
					D3 single does (one does of Vit D3 50,000 IU pre departure)		31	1.08 (sd=0.16)	final=1.08 (sd=0.15)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Burns et al., 2012	RCT/CCT	ND	ND	ND	Y	ND	ND	Y	Y	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Burris et al., 2012	Prospective Cohort	Pregnant or lactating women; White or Black race; fluency in English; gestational age <22 weeks	missing both second trimester maternal plasma and cord plasma		University and hospital	USA; Massachusetts	1303/1133/100	33 (4.5)/NR	Non-Hispanic White=82; Non-Hispanic Black=18	Not Reported	

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Burris et al., 2012	Prospective Cohort	none	Demographics (Age, Sex, Race/Ethnicity)- Maternal Age, Race; Anthropometrics- Prepregnancy BMI; Sun Exposure- Season Of Blood Draw	Secondary-Birth Weight	<25		47	NR (NR)	Final=3.46 (SD=0.68)		.
					25–50		314	NR (NR)	Final=3.55 (SD=0.52)		.
					50–75		543	NR (NR)	Final=3.53 (SD=0.51)		.
					>=75		229	NR (NR)	Final=3.51 (SD=0.52)		.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Burris et al., 2012	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Camargo et al., 2011	Prospective Cohort	0–6 months; cord blood available	Not specified		hospital	Wellington (41°S latitude) and Christchurch (43°S latitude), New Zealand	922/922/49	GA = 40 weeks (NR)/IQR: 39 – 41		Not Reported	

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Camargo et al., 2011	Prospective Cohort	NA	Demographics (Age, Sex, Race/Ethnicity)- Maternal Age At Birth, New Zealand Deprivation Index, Age, Gender, Child's Ethnicity; Medical Conditions- Maternal History Of Asthma, Paternal History Of Asthma; Sun Exposure- Study Site; Smoking, Other Lifestyle Factors- Smoking During Pregnancy, Passive Smoking; Other - Endotoxin On The Bedroom Floor, Damp Musty Smell In Any Room Of Home, Duration Of Exclusive Breastfeeding	Primary-Respiratory Infection	25(0H)D	>=75nmol/L-by 3months old	NR	NR/251	Adjusted/OR	1	reference	
					25(0H)D	25–74nmol/L-by 3months old	NR	NR/491	Adjusted/OR	1.35	0.88, 2.08	
					25(0H)D	<25nmol/L-by 3months old	NR	NR/180	Adjusted/OR	2.04	1.13, 3.67	0.03
				Primary-Any Infection	25(0H)D	>=75nmol/L-by 3months old	NR	NR/251	Adjusted/OR	1	reference	
					25(0H)D	25–74nmol/L-by 3months old	NR	NR/491	Adjusted/OR	1.49	0.92, 2.43	
					25(0H)D	<25nmol/L-by 3months old	NR	NR/180	Adjusted/OR	2.36	1.17, 4.73	0.02
				Primary-Wheeze	25(0H)D	per 10nmol/L-by 15months old	NR	331/922	Adjusted/OR	0.98	0.93, 1.02	0.3
					25(0H)D	per 10nmol/L-by 3years of age	NR	472/922	Adjusted/OR	0.96	0.91, 1.00	0.04
					25(0H)D	per 10nmol/L-by 5 years of age	NR	533/922	Adjusted/OR	0.95	0.91, 0.99	0.04
				Primary-Incident Asthma	25(0H)D	per 10nmol/L-by 5 years of age	NR	181/922	Adjusted/OR	1.03	0.97, 1.10	0.02

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Camargo et al., 2011	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	Y	N	B	Population a) sampling random Outcome c) primary outcome changed to NA

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Cauley et al., 2008	Nested Case Control	age, race or ethnicity, blood draw date	Other Nutrients Or Dietary Factors- Total Calcium Intake; Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking, Alcohol Use; Other - History Of Fracture, Oral Corticosteroid Use, Geographic Region	Primary-Hip Fractures	25(OH)D	Quartile 1: 9.2–47.5 nmol/L	7.1 yrs	NR/244	adjusted/OR	1.71	1.05, 2.79	
					25(OH)D	Quartile 2: 47.6–70.6 nmol/L	7.1 yrs	NR/195	adjusted/OR	1.09	0.70, 1.71	
					25(OH)D	Quartile 3: 60.2–70.6 nmol/L	7.1 yrs	NR/167	adjusted/OR	0.82	0.51, 1.31	
					25(OH)D	Quartile 4: 70.7–121.5 nmol/L	7.1 yrs	NR/193	adjusted/OR	1	Reference	
					25(OH)D	per 2.5 nmol/L decrease	7.1 yrs	NR/799	adjusted/OR	1.03	1.01, 1.05	0.015
					25(OH)D	per 25 nmol/L decrease	7.1 yrs	NR/799	adjusted/OR	1.33	1.06, 1.68	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Cauley et al., 2008	Y	Y	Y	N				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Cauley et al., 2011	Nested Case Control	19–50 years; 51–70 years; Postmenopausal women; aged 50–79; unlikely to move or die within 3 years; not enrolled in WHI clinical trial; not currently participating in any other clinical trial	Use of bisphosphonates, selective estrogen receptor modulators (SERMs), or tamoxifen; ‘‘other’’ or ‘‘unknown’’ race/ethnicity, current hormone therapy; missing important covariates	WHI OS	hospital and university	USA	2264/2232/100	64/50–70	Non-Hispanic White=34; Hispanic=17; Non-Hispanic Black=33; Asian=10; Race_other1=4	Post menopausal	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Cauley et al., 2011	Nested Case Control	age at screening, race/ethnicity, blood draw date	Other Nutrients Or Dietary Factors- Total Calcium Intake; Anthropometrics- Weight, Height; Medical Conditions- History Of Fracture; Smoking, Other Lifestyle Factors- Physical Activity	Primary-Fractures	25(OH)D	<20 ng/ml-whites	8.6 yrs	150/270	adjusted/OR	1	Reference	0.02
					25(OH)D	20–<30 ng/ml-whites	8.6 yrs	156/321	adjusted/OR	0.82	0.58, 1.16	
					25(OH)D	>=30 ng/ml-whites	8.6 yrs	84/189	adjusted/OR	0.56	0.35, 0.90	
					25(OH)D	<20 ng/ml-blacks	8.6 yrs	241/508	adjusted/OR	1	Reference	0.043
					25(OH)D	20–<30 ng/ml-blacks	8.6 yrs	108/193	adjusted/OR	1.48	1.05, 2.10	
					25(OH)D	>=30 ng/ml-Blacks	8.6 yrs	30/57	adjusted/OR	1.33	0.73, 2.43	
					25(OH)D	<20 ng/ml-Hispanics	8.6 yrs	89/182	adjusted/OR	1	Reference	0.72
					25(OH)D	20–<30 ng/ml-Hispanics	8.6 yrs	71/140	adjusted/OR	1.02	0.69, 1.79	
					25(OH)D	>=30 ng/ml-Hispanics	8.6 yrs	31/60	adjusted/OR	1.09	0.50, 2.37	
					25(OH)D	<20 ng/ml-Asians	8.6 yrs	37/80	adjusted/OR	1	Reference	0.22
					25(OH)D	20–<30 ng/ml-Asians	8.6 yrs	45/85	adjusted/OR	1.49	0.76, 2.93	
					25(OH)D	>=30 ng/ml-Asians	8.6 yrs	30/59	adjusted/OR	1.66	0.68, 4.02	
					25(OH)D	<20 ng/ml-native Americans	8.6 yrs	29/55	adjusted/OR	1	Reference	0.29
					25(OH)D	20–<30 ng/ml-native Americans	8.6 yrs	9/18	adjusted/OR	0.64	0.15, 2.79	
					25(OH)D	>=30 ng/ml-native Americans	8.6 yrs	6/15	adjusted/OR	0.43	0.09, 2.08	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Cauley et al., 2011	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	WHI observational study Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Cawthon et al., 2010	Prospective Cohort	51–70 years; walk without assistance, not have had bilateral hip replacement; >/= 65 years old	assay problem, insufficient sample for the vitamin D assay, missing data on covariates		Government	USA	1490/1490/0	74/>=65		Other; >80% Excellent/good health status	

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Cawthon et al., 2010	Prospective Cohort	NA	Other Nutrients Or Dietary Factors- Serum Calcium And Phosphate; Demographics (Age, Sex, Race/Ethnicity)- Age, Race, Education; Anthropometrics- Percentage Body Fat, Weight; Medical Conditions- GFR, Health Status, Presence Of At Least One Medical Condition; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Alcohol Use, Activity Level; Other - Marital Status, And Presence Of A Functional Or Mobility Limitation	Primary-Cancer Mortality	25(OH)D	Quartile 1: <19.9 ng/ml	7.3 yrs	NR/372	adjusted/HR	0.52	0.27, 1.00	0.086
					25(OH)D	Quartile 2: =19.9 to <25.2 ng/ml	7.3 yrs	NR/370	adjusted/HR	0.9	0.51, 1.60	
					25(OH)D	Quartile 3: =25.2 to <30.0 ng/ml	7.3 yrs	NR/372	adjusted/HR	0.8	0.45, 1.41	
					25(OH)D	Quartile 4: =30.0	7.3 yrs	NR/376	adjusted/HR	1	reference	
					25(OH)D	Deficient, <20 ng/ml	7.3 yrs	NR/376	adjusted/HR	0.51	0.27, 0.98	0.044
					25(OH)D	Insufficient, 20 to <30 ng/ml	7.3 yrs	NR/737	adjusted/HR	0.85	0.52, 1.40	
					25(OH)D	Sufficient, =30 ng/ml	7.3 yrs	NR/377	adjusted/HR	1	reference	
					25(OH)D	per SD decrease	7.3 yrs	NR/1490	adjusted/HR	0.8	0.64, 0.99	NR
				Primary-All-Cause Mortality	25(OH)D	Quartile 1: <19.9 ng/ml	7.3 yrs	NR/372	adjusted/HR	0.95	0.68, 1.34	0.961
					25(OH)D	Quartile 2: =19.9 to <25.2 ng/ml	7.3 yrs	NR/370	adjusted/HR	1.05	0.75, 1.47	
					25(OH)D	Quartile 3: =25.2 to <30.0 ng/ml	7.3 yrs	NR/372	adjusted/HR	0.89	0.64, 1.24	
					25(OH)D	Quartile 4: =30.0	7.3 yrs	NR/376	adjusted/HR	1	reference	
					25(OH)D	Deficient, <20 ng/ml	7.3 yrs	NR/376	adjusted/HR	0.94	0.67, 1.32	0.706
					25(OH)D	Insufficient, 20 to <30 ng/ml	7.3 yrs	NR/737	adjusted/HR	0.97	0.72, 1.30	
					25(OH)D	Sufficient, =30 ng/ml	7.3 yrs	NR/377	adjusted/HR	1	reference	
					25(OH)D	per SD decrease	7.3 yrs		adjusted/HR	1.01	0.89, 1.14	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Cawthon et al., 2010	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Cohen et al., 2013	Prospective Cohort	19–50 years; 51–70 years; 45–84 years old	Current cardiovascular disease; measured serum concentrations of 25(OH)D at the baseline MESA examination; serum 25(OH)D concentration suggestive of high-dose vitamin D supplementation (>100 ng/ml)	MESA	Government	USA; multiple	6436/6436/53	63.3 (10.2)/NR	Non-Hispanic White=586; Hispanic=186; Non-Hispanic Black=100; Race_other1= 128	Not Reported	Serum D: <20ng/ml group:14.0 (4.4) 20–29 ng/ml group-24.8 (3.8) >/=30ng/ml group-37.4 (7.2) Table 1 also gives D2 and D3 levels

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Cohen et al., 2013	Prospective Cohort	NA	Other Nutrients Or Dietary Factors- Vitamin D Intake; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race/Ethnicity, Education, Income; Anthropometrics- Body Mass Index; Medical Conditions- Diabetes, Chronic Kidney Disease; Smoking, Other Lifestyle Factors- Smoking Status; Other - Physical Activity, Systolic Blood Pressure, High-Density Lipoprotein Cholesterol, Low-Density Lipoprotein Cholesterol, Triglyceride Cholesterol, Parathyroid Hormone, And Natural Logarithm Of C-Reactive Protein Concentrations, Use Of Antihypertensives Or Lipid - Lowering Medications, Study Site	Primary-Incident Coronary Heart Disease Events	25(OH)D	<85.92	8.5 yrs	120/2131	adjusted/HR	1.32	0.95, 1.83	
					25(OH)D	85.92–124.58	8.5 yrs	134/2224	adjusted/HR	1.2	0.91, 1.58	
					25(OH)D	>=124.58	8.5 yrs	107/2081	adjusted/HR	1	reference	0.04
					25(OH)D	per 42.96 decrement	8.5 yrs	361/6436	adjusted/HR	1.15	1.01, 1.32	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Cohen et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Connor et al., 2012	Nested Case Control	51–70 years; >/= 65 years of age	Not specified		Government	USA; Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley near Pittsburgh, PA; Portland, OR; and San Diego, C	1746/777/0	74 (6)/NR	Non-Hispanic White=91	Overweight/obese; Other; diabetes = 10%; mild CKD (GFR<60 mL/min/1.73m3) =12%	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Connor et al., 2012	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Race; Anthropometrics- BMI; Medical Conditions- Self-Rated Health Condition, Kidney Function (EGFR), And History Of Diabetes; Sun Exposure- Latitude Of Study Site; Smoking, Other Lifestyle Factors- Physical Activity (PASE), Ever Smoked, Alcohol Drinks Per Week	Primary-Nonspine Fracture	25(OH)D	Normal level	4.6 yrs	100/594	adjusted/HR	1.2	0.8, 1.8	
					25(OH)D	Low vit D	4.6 yrs	34/183	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Connor et al., 2012	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	A	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Daly et al., 2009	RCT/CCT	51–70 years; Healthy; Caucasian; men; age >50 years; community-living	taken calcium-vitamin D supplements in the preceding 12 months; medication use known to affect bone metabolism; participated in regular resistance training in the previous 6 months or greater than 150 min per week of weight-bearing exercise; BMI > 35 kg/m2; lactose intolerance; consumed more than four alcoholic beverages per day; a history of osteoporotic fracture; medical disease or medication use known to affect bone metabolism		Manufacturer	Australia; Melbourne	167/124/0	61.2 (7.5)/NR	Non-Hispanic White=100		serum 25(OH)D milk group: 78 ± 23 nmol/l control group: 76 ± 23 nmol/l

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Daly et al., 2009	RCT/CCT	NR	Anthropometrics- Change In Weight; Smoking, Other Lifestyle Factors- Alcohol And Saturated Fat Intake	Secondary-DBP	D3 zxa		66	69.5 (sd=10.1)	change=4.2 (2.1, 6.2)	+0.3 (-2.6, 3.2)	.
					D3 control (no additional fortified milk)		58	71 (sd=9.8)	change=3.9 (2.0, 5.8)		.
				Secondary-SBP	D3 (400 ml reduced fact milk fortified with 1000 mg clacium+800 IU Vit D)/day		66	123.7 (sd=11.7)	change=6.8 (4.2, 9.3)	+1.5 (-2.4, 5.4)	.
					D3 control (no additional fortified milk)		58	120.4 (sd=12.1)	change=5.3 (2.4, 8.2)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Daly et al., 2009	RCT/CCT	ND	ND	Y	Y	ND	Y	Y	Y	Y	A	

ligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Dam et al., 2009	Prospective Cohort	30 years or greater; ambulatory; community dwelling; Caucasian	Not specified	Rancho Bernardo study	Government	USA; Southern California	1065/656/62	74.6 (10.3)/NR	Non-Hispanic White=98		Mean serum vitamin D concentration: men- 107.6±29.2 nmol/L, women- 100.8±33.1 nmol/L

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Dam et al., 2009	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Baseline Physical Activity Level, Alcohol Use	Secondary-Change In Grip Strength (Women)	25(OH)D 10–80 nmol/l		159	NR (NR)	Change= -0.78 (-4.76, 6.32)	+1.55 (NC)	0.22
					25(OH)D 82.5–97.5 nmol/l		181	NR (NR)	Change= -3.30 (-1.34, 7.95)	+5.63 (NC)	.
					25(OH)D 100–112.5 nmol/l		153	NR (NR)	Change= -2.01 (-6.85, 2.83)	+0.32 (NC)	.
					25(OH)D 115–337.5 nmol/l		163	NR (NR)	Change= -2.33 (-7.10, 2.45)	reference (reference)	.
				Secondary-Change In Grip Strength (Men)	25(OH)D 10–90 nmol/l		114	NR (NR)	Change= -0.71 (-2.12, 3.54)	+1.63 (NC)	0.22
					25(OH)D 92.5–102.5 nmol/l		86	NR (NR)	Change= -0.64 (-3.91, 2.63)	+1.7 (NC)	.
					25(OH)D 105–120 nmol/l		110	NR (NR)	Change= -0.37 (-2.34, 3.07)	+1.97 (NC)	.
					25(OH)D 122.5–262.5 nmol/l		99	NR (NR)	Change= -2.34 (-5.15, 0.48)	reference (reference)	.
				Secondary-Change In Timed Up And Go (Tug)(Women)	25(OH)D 10–80 nmol/l		159	NR (NR)	Change= 21.92 (16.22, 27.62)	+13.79 (NC)	0.002
					25(OH)D 82.5–97.5 nmol/l		181	NR (NR)	Change= 7.37 (2.69, 12.04)	-0.76 (NC)	.
					25(OH)D 100–112.5 nmol/l		153	NR (NR)	Change= 8.48 (3.48, 13.48)	+0.35 (NC)	.
					25(OH)D 115–337.5 nmol/l		163	NR (NR)	Change= 8.13 (3.16, 13.10)	reference (reference)	.
				Secondary-Change In Timed Up And Go (Tug) (Men)	25(OH)D 10–90 nmol/l		114	NR (NR)	Change= 3.36 (-1.11, 7.82)	+1.94 (NC)	0.99
					25(OH)D 92.5–102.5 nmol/l		86	NR (NR)	Change= 3.52 (-1.75, 8.79)	+2.1 (NC)	.
					25(OH)D 105–120 nmol/l		110	NR (NR)	Change= 4.95 (0.69, 9.21)	+3.53 (NC)	.
					25(OH)D 122.5–262.5 nmol/l		99	NR (NR)	Change= 1.42 (-3.05, 5.09)	reference (reference)	.

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
				Secondary-Change In Timed Chair Stands (TCS)(Women)	25(OH)D 10–80 nmol/l		159	NR (NR)	Change= 21.98 (16.28, 27.67)	+14.28 (NC)	0.002
					25(OH)D 82.5–97.5 nmol/l		181	NR (NR)	Change= 7.38 (2.70, 12.06)	-0.32 (NC)	.
					25(OH)D 100–112.5 nmol/l		153	NR (NR)	Change= 8.51 (3.51, 13.51)	+0.81 (NC)	.
					25(OH)D 115–337.5 nmol/l		163	NR (NR)	Change= 7.70 (2.58, 12.62)	reference (reference)	.
				Secondary-Change In Timed Chair Stands (TCS)(Men)	25(OH)D 10–90 nmol/l		114	NR (NR)	Change= 3.36 (-1.11, 7.82)	+1.94 (NC)	0.99
					25(OH)D 92.5–102.5 nmol/l		86	NR (NR)	Change= 3.52 (-1.75, 8.79)	+2.1 (NC)	.
					25(OH)D 105–120 nmol/l		110	NR (NR)	Change= 4.95 (0.69, 9.21)	+3.53 (NC)	.
					25(OH)D 122.5–262.5 nmol/l		99	NR (NR)	Change= 1.42 (-3.05, 5.09)	reference (reference)	.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Dam et al., 2009	N	Y	N	N						

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	N	NA	Y	Y	N	C	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Deo et al., 2011	Prospective Cohort	65 years or greater; not institutionalized; expected to remain in the community for at least 3 years; not under active treatment for cancer	Current cardiovascular disease; inadequate serum volume; able to provide informed written consent; taking lithium; history of primary hyperparathyroidism; implausible 25(OH)D concentrations	Cardiovascular Health Study	Government	USA; multiple	2283/2283/70	74 (4)/NR	Non-Hispanic Black=14		

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Deo et al., 2011	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race, Education; Anthropometrics- BMI; Medical Conditions- Hypertension, Diabetes Mellitus; Sun Exposure- Season, Clinic; Smoking, Other Lifestyle Factors- Physical Activity	Primary-Sudden Cardiac Death	25(OH)D	<20 ng/mL	14 yrs (median)	31/715	Adjusted/HR	1.47	0.88, 2.46	Not significant
					25(OH)D	>=20 ng/mL	14 yrs (median)	42/1568	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Deo et al., 2011	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	Y	N	A	reconciled - grade stays B --- Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Eaton et al., 2011	Nested Case Control	51–70 years; Postmenopausal women; 50–79 years	Current cancer; medications for bone loss (including bisphosphonates, calcitonin, and parathyroid hormone); history of ulcerative colitis or crown's disease; history of surgery to remove part of the intestine; use of a special diet for malabsorption, celiac sprue or ulcerative colitis; high blood calcium; medications that contained estrogen (up to 1 y before study entry; oral and dermal forms only), androgens (including anabolic steroids, dehydroepiandrosterone, and testosterone), selective estrogen receptor modulators, antiestrogens	WHI	Government	USA; multiple	2429/2429/100	65.1 (7.6)/NR	Non-Hispanic White=780; Hispanic=51; Non-Hispanic Black=132; Asian=16; Race_other1=10; Race_other2=12		quartiles

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Eaton et al., 2011	Nested Case Control	age, race/ethnicity, blood draw date, clinical center	Demographics (Age, Sex, Race/Ethnicity)- Age, Race; Anthropometrics- Waist Circumference, BMI; Medical Conditions- History Of Hypertension, Treated Diabetes, Cvd, Cancer; Sun Exposure- Month Of Blood Draw, Latitude; Smoking, Other Lifestyle Factors- Smoking Status, Weekly Alcohol Consumption, Physical Activity; Other - Breast And Colorectal Cancers, Cad-Trial Indicator, Systolic Blood Pressure	Primary-All-Cause Mortality	25(OH)D	Quartile 1: 3.25–36.50 nmol/L	10 yrs	NR/608	adjusted/HR	1.25	0.80–1.95	0.39
					25(OH)D	Quartile 2: 36.51–49.95 nmol/L	10 yrs	NR/606	adjusted/HR	1.13	0.73–1.75	
					25(OH)D	Quartile 3: 49.96–65.38 nmol/L	10 yrs	NR/608	adjusted/HR	1.17	0.75–1.81	
					25(OH)D	Quartile 4: 65.39–146.67 nmol/L	10 yrs	NR/607	adjusted/HR	1	Reference	
				Primary-Cardiovascular Disease Mortality	25(OH)D	Quartile 1: 3.25–36.50 nmol/L	10 yrs	NR/608	adjusted/HR	1.27	0.81, 1.99	0.33
					25(OH)D	Quartile 2: 36.51–49.95 nmol/L	10 yrs	NR/606	adjusted/HR	1.14	0.74, 1.78	
					25(OH)D	Quartile 3: 49.96–65.38 nmol/L	10 yrs	NR/608	adjusted/HR	1.16	0.75, 1.80	
					25(OH)D	Quartile 4: 65.39–146.67 nmol/L	10 yrs	NR/607	adjusted/HR	1	Reference	
				Primary-Cancer Mortality	25(OH)D	Quartile 1: 3.25–36.50 nmol/L	10 yrs	NR/608	adjusted/HR	1.39	0.88, 2.19	0.11
					25(OH)D	Quartile 2: 36.51–49.95 nmol/L	10 yrs	NR/606	adjusted/HR	1.22	0.79, 1.89	
					25(OH)D	Quartile 3: 49.96–65.38 nmol/L	10 yrs	NR/608	adjusted/HR	1.12	0.72, 1.72	
					25(OH)D	Quartile 4: 65.39–146.67 nmol/L	10 yrs	NR/607	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Eaton et al., 2011	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	A	WHI observational study Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Eliassen et al., 2011	Prospective Cohort	19–50 years; 51–70 years	Current cancer	NHSII	Government	USA; multiple	1831/1831/100	44.9 (4.4)/NR			serum vitamin D: cases 63.4±23.7nmol/L, controls-62.4±24.0 nmol/L

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Eliassen et al., 2011	Prospective Cohort	age (± 2 years); menopausal status at diagnosis; month/year of collection (± 2 months); ethnicity (African-American, Asian, Hispanic, Caucasian, Other); luteal day ((date of next period-date of luteal blood draw) ± 1 day); and for each blood collection, t	Anthropometrics- BMI At Blood Collection; Sun Exposure- Season Of Blood Collection; Smoking, Other Lifestyle Factors- Physical Activity; Other - Premenopausal, Time Of Diagnosis Relative To Blood Collection, Age At Blood Collection, Family History Of Breast Cancer, Luteal Phase Of Premenopausal Women	Primary-Breast Cancer	25(0H)D	Quartile 1(<18.4ng/mL)	NR	141/441	adjusted/RR	1	reference	
					25(0H)D	Quartile 2(18.4 to 24.6ng/m)	NR	151/456	adjusted/RR	1.05	0.79, 1.39	
					25(0H)D	Quartile 3(24.6 to <30.6ng/m)	NR	145/452	adjusted/RR	0.95	0.71, 1.29	
					25(0H)D	Quartile 4 (>=30.6ng/mL)	NR	176/482	adjusted/RR	1.2	0.88, 1.63	0.320
				Primary-Invasive Breast Cancer	25(0H)D	Quartile 1(<18.4ng/mL)	NR	95/395	adjusted/RR	1	reference	
					25(0H)D	Quartile 2(18.4 to 24.6ng/m)	NR	98/403	adjusted/RR	1.03	0.74, 1.44	
					25(0H)D	Quartile 3(24.6 to <30.6ng/m)	NR	97/404	adjusted/RR	1.01	0.72, 1.42	
					25(0H)D	Quartile 4 (>=30.6ng/mL)	NR	125/431	adjusted/RR	1.29	0.92, 1.81	0.140

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Eliassen et al., 2011	N	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	cases of breast cancer were reported on biennial questionnaires and confirmed by medical record review or verbal confirmation by the nurse -- - Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Engel et al., 2010	Nested Case Control	born between 1925 and 1950; French women	Not specified	French E3N cohort	Government	France	1908/1833/100	56.9 (6.4)/NR			serum vitamin D: cases- 24.4+/-10.9 ng/ml, control- 25.1+/-11.0 ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Engel et al., 2010	Nested Case Control	age (±2 years), menopausal status at blood collection, age at menopause (±2 years), study center, date of blood collection (same year)	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Other - Dietary Calcium Intake	Primary-Breast Cancer	25(0H)D	<19.8 ng/mL	<=10 years	226/630	adjusted/OR	1	reference	
					25(0H)D	19.8–27ng/mL	<=10 years	198/600	adjusted/OR	0.81	0.63, 1.04	
					25(0H)D	>27ng/mL	<=10 years	191/603	adjusted/OR	0.73	0.55, 0.96	0.020

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Engel et al., 2010	N	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Fedirko et al., 2012	Nested Case Control	Not specified	Not specified	EPIC	Government	Multiple Countries	1202/1202/59.5	62.1 (7.2)/NR			by quintiles

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Fedirko et al., 2012	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Age At Diagnosis, Sex; Anthropometrics- BMI; Medical Conditions- Cancer Stage, Grade Of Tumor Differentiation, Location Of Primary Tumor; Sun Exposure- Season Of Blood Collection; Smoking, Other Lifestyle Factors- Smoking Status, Physical Activity; Other - Year Of Diagnosis	Primary-Colorectal Cancer Specific Mortality	25(OH)D	Quintile 1:<36.3	73 mos	104/242	adjusted/HR	1	Reference	0.04
					25(OH)D	Quintile 2:36.4–48.6	73 mos	85/239	adjusted/HR	0.76	0.56, 1.02	
					25(OH)D	Quintile 3:48.7–60.5	73 mos	95/241	adjusted/HR	0.93	0.69, 1.24	
					25(OH)D	Quintile 4:60.6–76.8	73 mos	78/240	adjusted/HR	0.78	0.58, 1.06	
					25(OH)D	Quintile 5:>76.8	73 mos	82/240	adjusted/HR	0.69	0.50, 0.93	
				Primary-Overall Mortality	25(OH)D	Quintile 1:<36.3	73 mos	128/242	adjusted/HR	1	Reference	<0.01
					25(OH)D	Quintile 2:36.4–48.6	73 mos	108/239	adjusted/HR	0.82	0.63, 1.07	
					25(OH)D	Quintile 3:48.7–60.5	73 mos	117/241	adjusted/HR	0.91	0.70, 1.18	
					25(OH)D	Quintile 4:60.6–76.8	73 mos	95/240	adjusted/HR	0.78	0.59, 1.03	
					25(OH)D	Quintile 5:>76.8	73 mos	93/240	adjusted/HR	0.67	0.50, 0.88	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Fedirko et al., 2012	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	B	Sampling was random

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Fiscella et al., 2010	Prospective Cohort	Not specified	Not specified	NHANES-III	Government		15,363/15363/ 52	43.64/NR	Non-Hispanic White=77; Hispanic=9; Non-Hispanic Black=10; Race_other1= 3		serum vitamin D: 29.5 ng/ml

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Fiscella et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Log (Age), Sex, Race/Ethnicity; Anthropometrics- BMI Category; Medical Conditions- Self-Reported Diabetes, Cvd; Sun Exposure- Interview Month, Region; Smoking, Other Lifestyle Factors- Currently Smoking Or Not, Physical Inactivity; Other - Self-Rated Health, Systolic Blood Pressure, EGFR, Total Cholesterol, Serum Albumin, CRP, Urinary Acr	Primary- Cardiovascular Death	25(OH)D	Q1: <18 ng/mL	138,549 person years	933/15363	Adjusted/IRR	1	Reference	
					25(OH)D	Q2: 18–24.9 ng/mL	138,549 person years		Adjusted/IRR	0.71	0.54, 0.94	NR
					25(OH)D	Q3: 25–31.9 ng/mL	138,549 person years		Adjusted/IRR	0.65	0.53, 0.79	NR
					25(OH)D	Q4: >32 ng/mL	138,549 person years		Adjusted/IRR	0.79	0.62, 1.01	NR
					25(OH)D	<18 ng/mL	138,549 person years	933/15363	Adjusted/IRR	1.4	1.16, 1.69	<0.001
					25(OH)D	>=18 ng/mL	138,549 person years		Adjusted/IRR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Fiscella et al., 2010	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	Sampling was random

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Forman et al., 2013	RCT/CCT	19–50 years; 51–70 years; Able to participate, understand English..; 30–80 years; written and spoken English; self-identified as black; with permission from primary care doctors	Current cancer; disorders of calcium metabolism or parathyroid function; type 1 diabetes; sarcoidosis; active malignancy other than non-melanoma skin cancer; active thyroid disease; cognitive impairment; plan on traveling to a sunny region during the supplementation phase of the study		Government	USA; Boston, MA	283/283/65.4	51/44–59	Hispanic=67; Non-Hispanic Black=933		Median serum vitamin D-15.7 (10.7–23.4 IQR) ng/ml

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Forman et al., 2013	RCT/CCT	NR	NR	Secondary-Diastolic Blood Pressure	D3 Vit D3 1000 IU/day		68	79.8 (se=1.3)	final=78.0 (se=1.6)	-0.9 (-5.7, 3.9)	0.71
					D3 Vit D3 2000 IU/day		73	77.6 (se=1.4)	final=76.0 (se=1.8)	-2.9 (-7.9, 2.1)	0.26
					D3 Vit D3 4000 IU/day		70	79.8 (se=1.6)	final=78.0 (se=1.6)	-0.9 (-5.7, 3.9)	0.71
					D3 placebo		72	78 (se=1.3)	final=78.9 (se=1.8)		.
				Secondary-Systolic Blood Pressure	D3 Vit D3 1000 IU/day		68	124.7 (se=2.1)	final=122.5 (se=2.0)	-2.4 (-8.6, 3.8)	0.45
					D3 Vit D3 2000 IU/day		73	122.8 (se=2.0)	final=120.0 (se=2.4)	-4.9 (-11.6, 1.8)	0.15
					D3 Vit D3 4000 IU/day		70	130.4 (se=2.4)	final=126.6 (se=2.6)	+1.7 (-5.3, 8.7)	0.63
					D3 placebo		72	122.2 (se=2.2)	final=124.9 (se=2.4)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Forman et al., 2013	RCT/CCT	Y	ND	Y	ND	Y	ND	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Formiga et al., 2014	Prospective Cohort	community dwelling adults born in 1924	Not specified	Octabaix	Unclear	Spain	312/312/60.6	85 (0)/NR		Other; Oldest old	70 ± 75 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Formiga et al., 2014	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Sex, Educational Level, Marital Status; Medical Conditions- Charlton Index; Other - Barthel Index (Physical Performance), MEC (Cognitive Performance)	Primary-Total Mortality	25(OH)D	Q1: <34.94	2.8 yrs	15/71	unadjusted/HR	1.28	0.61, 2.6	0.41
					25(OH)D	Q2: 34.94–61.65	2.8 yrs	18/77	unadjusted/HR	1.36	0.67, 2.74	
					25(OH)D	Q3: 61.66–83.37	2.8 yrs	11/84	unadjusted/HR	0.76	0.34, 1.68	
					25(OH)D	Q4:>83.37	2.8 yrs	14/80	unadjusted/HR	1	Reference	
				Primary-Cardiovascular Mortality	25(OH)D	Q1: <34.94	2.8 yrs	6/71	unadjusted/HR	1.04	0.33, 3.24	0.86
					25(OH)D	Q2: 34.94–61.65	2.8 yrs	6/77	unadjusted/HR	0.89	0.28, 2.80	
					25(OH)D	Q3: 61.66–83.37	2.8 yrs	6/84	unadjusted/HR	1.47	0.45, 4.58	
					25(OH)D	Q4:>83.37	2.8 yrs	7/80	unadjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Formiga et al., 2014	N	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Freedman et al., 2010	Prospective Cohort	19–50 years; 51–70 years; 17 years and older; completed MEC exam	no 25(OH)D; unknown mortality status	NHANES-III	Government	USA; multiple	16,819/NR/12.2	44.5/NR	Non-Hispanic White=5; Hispanic=124; Non-Hispanic Black=338; Race_other1=144		

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Freedman et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race/Ethnicity; Anthropometrics- BMI; Sun Exposure- Season/ Latitude; Smoking, Other Lifestyle Factors- Smoking History	Primary-Total Cancer Mortality	25(OH)D	< 37.5 nmol/L-men and women, all seasons	13.4 yrs	116/NR	adjusted/RR	1	Reference	0.43
					25(OH)D	37.5–<50 nmol/L-men and women, all seasons	13.4 yrs	174/NR	adjusted/RR	1.04	0.77, 1.41	
					25(OH)D	50 –<62.5 nmol/L-men and women, all seasons	13.4 yrs	165/NR	adjusted/RR	1.23	0.89, 1.69	
					25(OH)D	62.5–80 nmol/L-men and women, all seasons	13.4 yrs	200/NR	adjusted/RR	1.19	0.86, 1.65	
					25(OH)D	80–<100 nmol/L-men and women, all seasons	13.4 yrs	139/NR	adjusted/RR	1.12	0.80, 1.57	
					25(OH)D	>=100 nmol/L-men and women, all seasons	13.4 yrs	90/NR	adjusted/RR	1.15	0.79, 1.68	
					25(OH)D	< 37.5 nmol/L-men & women, winter/lower latitude	13.4 yrs	55/NR	adjusted/RR	1	Reference	0.23
					25(OH)D	37.5–<50 nmol/L-men & women, winter/lower latitude	13.4 yrs	79/NR	adjusted/RR	1.3	0.77, 2.19	
					25(OH)D	50 –<62.5 nmol/L-men & women, winter/lower latitude	13.4 yrs	57/NR	adjusted/RR	1.2	0.64, 2.26	
					25(OH)D	62.5–80 nmol/L-men & women, winter/lower latitude	13.4 yrs	78/NR	adjusted/RR	1.67	0.98, 2.86	
					25(OH)D	80–<100 nmol/L-men & women, winter/lower latitude	13.4 yrs	54/NR	adjusted/RR	1.31	0.77, 2.23	
					25(OH)D	>=100 nmol/L-men & women, winter/lower latitude	13.4 yrs	32/NR	adjusted/RR	1.5	0.74, 3.02	
					25(OH)D	< 37.5 nmol/L-men & women, summer/higher latitude	13.4 yrs	61/NR	adjusted/RR	1	Reference	0.67
					25(OH)D	37.5–<50 nmol/L-men & women, summer/higher latitude	13.4 yrs	95/NR	adjusted/RR	0.91	0.63, 1.32	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	50 –<62.5 nmol/L-men & women, summer/higher latitude	13.4 yrs	108/NR	adjusted/RR	1.19	0.78, 1.82	
					25(OH)D	62.5–80 nmol/L-men & women, summer/higher latitude	13.4 yrs	122/NR	adjusted/RR	1.02	0.67, 1.54	
					25(OH)D	80–<100 nmol/L-men & women, summer/higher latitude	13.4 yrs	85/NR	adjusted/RR	1.03	0.66, 1.63	
					25(OH)D	>=100 nmol/L-men & women, summer/higher latitude	13.4 yrs	58/NR	adjusted/RR	1.02	0.63, 1.45	
					25(OH)D	< 37.5 nmol/L-men, all seasons	13.4 yrs	47/NR	adjusted/RR	1	Reference	0.09
					25(OH)D	37.5–<50 nmol/L-men, all seasons	13.4 yrs	95/NR	adjusted/RR	1.66	0.98, 2.80	
					25(OH)D	50 –<62.5 nmol/L-men, all seasons	13.4 yrs	90/NR	adjusted/RR	1.43	0.90, 2.26	
					25(OH)D	62.5–80 nmol/L-men, all seasons	13.4 yrs	122/NR	adjusted/RR	1.52	0.82, 2.80	
					25(OH)D	80–<100 nmol/L-men, all seasons	13.4 yrs	90/NR	adjusted/RR	1.66	1.06, 2.61	
					25(OH)D	>=100 nmol/L-men, all seasons	13.4 yrs	69/NR	adjusted/RR	1.85	1.02, 3.35	
					25(OH)D	< 37.5 nmol/L-men, winter/lower latitude	13.4 yrs	25/NR	adjusted/RR	1	Reference	0.55
					25(OH)D	37.5–<50 nmol/L-men, winter/lower latitude	13.4 yrs	51/NR	adjusted/RR	2.58	1.37, 4.87	
					25(OH)D	50 –<62.5 nmol/L-men, winter/lower latitude	13.4 yrs	31/NR	adjusted/RR	1.14	0.48, 2.70	
					25(OH)D	62.5–80 nmol/L-men, winter/lower latitude	13.4 yrs	52/NR	adjusted/RR	1.99	0.86, 4.13	
					25(OH)D	80–<100 nmol/L-men, winter/lower latitude	13.4 yrs	33/NR	adjusted/RR	1.42	0.74, 2.72	
					25(OH)D	>=100 nmol/L-men, winter/lower latitude	13.4 yrs	23/NR	adjusted/RR	1.94	0.69, 5.45	
					25(OH)D	< 37.5 nmol/L-men, summer/higher latitude	13.4 yrs	22/NR	adjusted/RR	1	Reference	0.045

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	37.5–<50 nmol/L-men, summer/higher latitude	13.4 yrs	44/NR	adjusted/RR	1.28	0.51, 3.23	
					25(OH)D	50 –<62.5 nmol/L-men, summer/higher latitude	13.4 yrs	59/NR	adjusted/RR	1.55	0.81, 2.99	
					25(OH)D	62.5–80 nmol/L-men, summer/higher latitude	13.4 yrs	70/NR	adjusted/RR	1.33	0.53, 3.53	
					25(OH)D	80–<100 nmol/L-men, summer/higher latitude	13.4 yrs	57/NR	adjusted/RR	1.76	0.87, 3.57	
					25(OH)D	>=100 nmol/L-men, summer/higher latitude	13.4 yrs	46/NR	adjusted/RR	1.84	0.85, 3.98	
					25(OH)D	< 37.5 nmol/L-women, all seasons	13.4 yrs	69/NR	adjusted/RR	1	Reference	0.29
					25(OH)D	37.5–<50 nmol/L-women, all seasons	13.4 yrs	79/NR	adjusted/RR	0.85	0.59, 1.22	
					25(OH)D	50 –<62.5 nmol/L-women, all seasons	13.4 yrs	75/NR	adjusted/RR	1.25	0.82, 1.90	
					25(OH)D	62.5–80 nmol/L-women, all seasons	13.4 yrs	78/NR	adjusted/RR	1.11	0.69, 1.79	
					25(OH)D	80–<100 nmol/L-women, all seasons	13.4 yrs	49/NR	adjusted/RR	0.86	0.50, 1.46	
					25(OH)D	>=100 nmol/L-women, all seasons	13.4 yrs	21/NR	adjusted/RR	0.64	0.35, 1.18	
					25(OH)D	< 37.5 nmol/L-women, winter/lower latitude	13.4 yrs	30/NR	adjusted/RR	1	Reference	0.42
					25(OH)D	37.5–<50 nmol/L-women, winter/lower latitude	13.4 yrs	28/NR	adjusted/RR	0.74	0.36, 1.51	
					25(OH)D	50 –<62.5 nmol/L-women, winter/lower latitude	13.4 yrs	26/NR	adjusted/RR	1.27	0.51, 3.18	
					25(OH)D	62.5–80 nmol/L-women, winter/lower latitude	13.4 yrs	26/NR	adjusted/RR	1.44	0.61, 3.38	
					25(OH)D	80–<100 nmol/L-women, winter/lower latitude	13.4 yrs	21/NR	adjusted/RR	1.28	0.50, 3.24	
					25(OH)D	>=100 nmol/L-women, winter/lower latitude	13.4 yrs	9/NR	adjusted/RR	1.01	0.26, 3.90	
					25(OH)D	< 37.5 nmol/L-women, summer/higher latitude	13.4 yrs	39/NR	adjusted/RR	1	Reference	0.03
					25(OH)D	37.5–<50 nmol/L-women, summer/higher latitude	13.4 yrs	51/NR	adjusted/RR	0.88	0.54, 1.43	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	50 –<62.5 nmol/L-women, summer/higher latitude	13.4 yrs	49/NR	adjusted/RR	1.18	0.65, 2.12	
					25(OH)D	62.5–80 nmol/L-women, summer/higher latitude	13.4 yrs	52/NR	adjusted/RR	0.99	0.52, 1.87	
					25(OH)D	80–<100 nmol/L-women, summer/higher latitude	13.4 yrs	28/NR	adjusted/RR	0.7	0.34, 1.44	
					25(OH)D	>=100 nmol/L-women, summer/higher latitude	13.4 yrs	12/NR	adjusted/RR	0.52	0.25, 1.10	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Freedman et al., 2010	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	B	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Ganmaa et al., 2012	RCT/CCT	9–18 years; 12–15 years; residing in Ulaanbaatar	Not specified		Manufacturer	China ;Ulaanbaatar, Mongolia	120/117/47.5	13.1 (1.5)/NR		Other; latent tuberculosis	18+/-10 nmol/L

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Ganmaa et al., 2012	RCT/CCT	NR	NR	Primary-Tuberculin Skin Test(Tst)	Vit D	800IU/day-NR	NR	17/59	Adjusted/RR	0.41	0.16, 1.09	0.06
					Vit D	Placebo-NR	NR	24/58	Adjusted/RR	1	reference	

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Ganmaa et al., 2012	RCT/CCT	Y	Y	ND	Y	Y	N	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Gepner et al., 2012	RCT/CCT	Postmenopausal women; Healthy; serum 25(OH)D concentrations between 10–60ng/ml; community dwelling; ambulatory	use of medications that interfere with vitamin D metabolism or affect bone turn over; active metabolites of vitamin D within 6 months of screening; history of CVD; serum calcium >10.5mg/dl; untreated hyperparathyroidism; history of nephrolithiasis, hypercalciuria, malignancy, tuberculosis, sarcoidosis; Paget's disease; malabsorption syndromes; estimated glomerular filtration rate</=25 mL/minute; use of tanning beds or salons, unwilling to use sunscreen during periods of sun exposure >15 minutes		university	USA; Madison, WI	114/114/100	63.9 (3.0)/NR		Post menopausal	serum vitamin D- 31.3+/- 10.6 ng/ml

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Gepner et al., 2012	RCT/CCT	NR	Anthropometrics- BMI	Secondary-Brachial DBP	D3 placebo		57	72.6 (sd=7.1)	change=-0.4 (sd=4.4)		.
					D3 Vit D3 2500 IU/day		57	72.45 (sd=7.6)	change=-0.7 (sd=5.1)	-0.3 (-2.1, 1.5)	0.73
				Secondary-Brachial SBP	D3 placebo		57	122.2 (sd=11.8)	change=-2.5 (sd=10.9)		.
					D3 Vit D3 2500 IU/day		57	122.3 (sd=13.1)	change=-0.3 (sd=8.4)	+2.2 (-1.4, 5.8)	0.23
				Secondary-Central DBP	D3 placebo		57	73.7 (sd=7.1)	change=-0.5 (sd=4.4)		.
					D3 Vit D3 2500 IU/day		57	73.5 (sd=7.7)	change=-0.7 (sd=5.1)	-0.2 (-2.0, 1.6)	0.82
				Secondary-Central SBP	D3 placebo		57	115.6 (sd=11.1)	change=-2.1 (sd=9.7)		.
					D3 Vit D3 2500 IU/day		57	116.7 (sd=12.2)	change=-0.3 (sd=7.0)	+1.8 (-1.3, 4.9)	0.26

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Gepner et al., 2012	RCT/CCT	Y	Y	Y	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Gernand et al., 2013	Prospective Cohort	Pregnant or lactating women; singleton gestation; white, black or Puerto Rican maternal race/ethnicity; entry to prenatal care at 26 weeks or less; available stored serum sample at 26 weeks or less	Hypertension; Type 2 DM; diabetes; stillbirth; preterm birth; serum unsuitable for vitamin d measurement; missing covariates	Collaborative Perinatal Project	Government	USA; multiple	2146/2146/100	NR/NR	Non-Hispanic White=521; Hispanic=63; Non-Hispanic Black=416	Other; pregnant	maternal serum vitamin D: 51.3+/-28.0 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Gernand et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Maternal Race/Ethnicity; Anthropometrics- Prepregnancy BMI, Height; Sun Exposure- Season And Study Site; Smoking, Other Lifestyle Factors- Smoking	Secondary-Birth Weight	<37.5		747	NR (NR)	Final=3127 (SD=15)		.
					>=37.5		1399	NR (NR)	Final=3215 (SD=11)		.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Gernand et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Ginde et al., 2009	Prospective Cohort	>/= 65 years; Non-institutionalized US civilian population	Not specified	NHANES III	Government	USA; multiple	3408/3408/56	73 (0.2)/NR	Non-Hispanic White=87; Hispanic=2; Non-Hispanic Black=7; Race_other1=4		median 25(OH) D level-66.0 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Ginde et al., 2009	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race/Ethnicity; Anthropometrics- BMI; Medical Conditions- Asthma, Copd, Hypertension, Diabetes, Hyperlipidemia; Sun Exposure-Season; Smoking, Other Lifestyle Factors- Physical Activity, Smoking Status, Cigarette Pack Years; Other - Region, Renal Function, History Of MI, Stroke, Cancer (Nonskin)	Secondary-Cardiovascular Death	25(OH)D	<25.0 nmol/L	7.3 yrs	767/115	Adjusted/HR	2.36	1.17, 4.75	<0.05
					25(OH)D	25.0–49.9 nmol/L	7.3 yrs	NR/904	Adjusted/HR	1.54	1.01, 2.34	<0.05
					25(OH)D	50.0–74.9 nmol/L	7.3 yrs	NR/1296	Adjusted/HR	1.26	0.85, 1.88	NS
					25(OH)D	75.0–99.9 nmol/L	7.3 yrs	NR/775	Adjusted/HR	1.2	0.79, 1.81	NS
					25(OH)D	>=100.0 nmol/L	7.3 yrs	NR/318	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Ginde et al., 2009	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	B	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Goldring et al., 2013	RCT/CCT	0–6 months; 7 months–2 years; 3–8 years; children 0–3 years of age; mothers participated in vitamin D RCT from 27 weeks gestation; black, white, Asian or middle eastern	known sarcoidosis, osteomalacia, renal dysfunction, tuberculosis		Private Foundation	UK	180/106/56	3/NR	Non-Hispanic White=26; Non-Hispanic Black=24; Asian=24; Race_other1= 26	Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Goldring et al., 2013	RCT/CCT	Not applicable	Other Nutrients Or Dietary Factors- Vitamin Supplementation; Demographics (Age, Sex, Race/Ethnicity)- Maternal Ethnicity, Maternal Education; Smoking, Other Lifestyle Factors- Smokers In Household, Maternal Smoking During Pregnancy; Other - Family History Of Allergy, Number Of Children In Household, Baseline Maternal 25(Oh)d	Primary-Wheeze Ever	D	either 800 IU ergocalciferol daily or 200,000 IU calciferol (single dose)	3 yrs	11/56	adjusted/OR	0.56	0.20, 1.57	0.27
						control	3 yrs	14/50	adjusted/OR	1	reference	
				Secondary-Lower Respiratory Tract Infection	D	either 800 IU ergocalciferol daily or 200,000 IU calciferol (single dose)	3 yrs	14/54	adjusted/OR	1	0.35, 2.91	1
						control	3 yrs	11/50	adjusted/OR	1	reference	

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Goldring et al., 2013	RCT/CCT	Y	Y	NA	Y	Y	N	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Green et al., 2010	Nested Case Control	Postmenopausal women; nurses; no history of cancer at the time of blood sample	Not specified	Nurses' Health Study	Government	USA; multiple	960/469/100	61.0/NR		Post menopausal	tertiles

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Green et al., 2010	Nested Case Control	age +/- 2years, fasting status at the time of blood collection, and PMH use, month of blood collection, time of day that blood was drawn (62 hr)	Demographics (Age, Sex, Race/Ethnicity)- Age At Mammography; Smoking, Other Lifestyle Factors- Alcohol Intake, Smoking Status; Other - Personal History Of Benign Breast Disease, Age At Menarche, Parity, Age At First Birth, Use Of Postmenopausal Hormones, Age At Menopause	Secondary-Percent Mammographic Density	1,25(OH)2D: 1st quartile (13.0–29.1 ng/ml)		110	NR (NR)	final=25.5 (NR)		.
					1,25(OH)2D: 2nd quartile (29.2–33.1 ng/ml)		108	NR (NR)	final=27.6 (NR)	+2.1 (NC)	.
					1,25(OH)2D: 3rd quartile (33.2–37.3 ng/ml)		110	NR (NR)	final=23.3 (NR)	-2.2 (NC)	.
					1,25(OH)2D: 4th quartile (37.4–56.2 ng/ml)		114	NR (NR)	final=25.8 (NR)	+0.3 (NC)	.
					25(OH)D: 1st quartile (cut points vary by batches)		118	NR (NR)	final=26.3 (NR)		.
					25(OH)D: 2nd quartile		115	NR (NR)	final=25.6 (NR)	-0.7 (NC)	.
					25(OH)D: 3rd quartile		124	NR (NR)	final=24.8 (NR)	-1.5 (NC)	.
					25(OH)D: 4th quartile		112	NR (NR)	final=25.7 (NR)	-0.6 (NC)	.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Green et al., 2010	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	medical record reviews were used to confirm breast cancer diagnoses but article did not state whether diagnoses were verified independently Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Grimnes et al., 2012	RCT/CCT	19–50 years; 51–70 years; Postmenopausal women; 50–80 years; T-score in total hip or lumbar spine (L2–4)=-2.0	Current cancer; Current cardiovascular disease; Type 2 DM; hormone replacement therapy or other therapy affecting bone remodeling during the last 12 months before enrollment; use of steroids; renal stone disease; systolic blood pressure >175mmHg or diastolic blood pressure >105mmHg; serum creatinine >110 µmol/l; suspected hyperparathyroidism; chronic disease like ischemic heart disease, diabetes, granulomatous disease, and cancer		Manufacturer	Norway	297/297/100	63.5 (6.8)/NR		Post menopausal	serum vitamin D: high dose group- 70.7+/-23.0 nmol/L; standard dose group- 71.2+/-22.3 nmol/L

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Grimnes et al., 2012	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Sun Exposure- Reported Outdoor Time, Sunny Holidays, Sun Bed Use; Smoking, Other Lifestyle Factors- Smoking, Physical Activity	Secondary-Total Hip BMD	D3 high dose (6500 IU/day)+1000 mg elemental calcium/day-overall		149	0.79 (sd=0.073)	change=0.31 (sd=1.59)	-0.25 (-0.63, 0.13)	0.19
					D3 standard dose(800 IU/day)+1000 mg elemental calcium/day-overall		148	0.791 (sd=0.082)	change=0.56 (sd=1.70)		.
				Secondary-Femoral Neck BMD	D3 high dose (6500 IU/day)+1000 mg elemental calcium/day-overall		149	0.758 (sd=0.066)	change=0.03 (sd=2.08)	-0.14 (-0.59, 0.31)	.
					D3 standard dose(800 IU/day)+1000 mg elemental calcium/day-overall		148	0.757 (sd=0.079)	change=0.17 (sd=1.87)		.
				Secondary-L2-L4 BMD	D3 high dose (6500 IU/day)+1000 mg elemental calcium/day-overall		149	0.901 (sd=0.072)	change=0.25 (sd=3.19)	-0.07 (-0.80, 0.66)	.
					D3 standard dose(800 IU/day)+1000 mg elemental calcium/day-overall		148	0.902 (sd=0.079)	change=0.32 (sd=3.23)		.
				Secondary-Total Body BMD	D3 high dose (6500 IU/day)+1000 mg elemental calcium/day-overall		149	1 (sd=0.054)	change=0.18 (sd=1.14)	-0.02 (-0.29, 0.25)	.
					D3 standard dose(800 IU/day)+1000 mg elemental calcium/day-overall		148	1.002 (sd=0.055)	change=0.20 (sd=1.23)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Grimnes et al., 2012	RCT/CCT	Y	Y	Y	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Holland et al., 2012	RCT/CCT	0–6 months; 7 months–2 years; infants aged 1–11 months; living within the socioeconomically deprived study districts	vitamin D within previous 3 months; families expecting to move to another town within 18 months; rickets; clinical diagnosis of Kwashiorkor or Marasmus		Private Foundation	Kabul, Afghanistan	3046/NR/48	NR/NR		Malnourished/frailty	only box plot of figure 3

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Holland et al., 2012	RCT/CCT	NR	NR	Primary-All Pneumonia First Episode	Vit D3	100,000IU-confirmed chest radiograph confirmed	NR	260/NR	Adjusted/IRR	1.065	0.895, 1.268	0.476
						Placebo-confirmed chest radiograph confirmed	NR	2445/NR	Adjusted/IRR	1	reference	
				Primary-All Pneumonia Repeat Episode	Vit D3	100,000IU-confirmed chest radiograph confirmed	NR	138/NR	Adjusted/IRR	1.685	1.282, 2.212	<0.0001
						Placebo-confirmed chest radiograph confirmed	NR	82/NR	Adjusted/IRR	1	reference	

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Holland et al., 2012	RCT/CCT	Y	ND	Y	N	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Hollis et al., 2011	RCT/CCT	Pregnant or lactating women; maternal age of 16 years or greater at the time of consent; confirmed singleton pregnancy of fewer than 16 completed weeks of gestation at the time of consent; planned to receive ongoing prenatal care in the Charleston, SC, area,; ability to provide written informed consent at the first visit.	required chronic diuretic or cardiac medication therapy, including calcium channel blockers; suffered chronic hypertension; Pregnant women with preexisting calcium or parathyroid conditions; Women with a pregnancy at greater than 16 weeks of gestation as calculated by their last menstrual period; active thyroid disease		Government	USA; Charleston, SC	502/350/100	27.0 (5.6)/18–41	Non-Hispanic White=342; Hispanic=405; Non-Hispanic Black=252		serum: delivered group- 59.5.8 nmol/L (6.0–172.5) exited group- 50.5.1nmol/L (6.5–120.5) vit D intake: 400 IU group- 181.6+/-108.4 IU/d, 2000 IU group- 195.8+/-135.0, 4000 IU group- 204.2+/-148.2 calcium intake: 400 IU group-1063.6+/-539.6 mg

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Hollis et al., 2011	RCT/CCT	NR	NR	Secondary-Birth Weight	Vit D 4000 IU		117	NR (NR)	Final=3284.6 (3175.2, 3394.0)	+62.8 (-103.4, 229.0)	0.23
					Vit D 2000 IU		122	NR (NR)	Final=3360.1 (3255.2, 3465.0)	+138.3 (-24.4, 301.0)	.
					Vit D 400 IU		111	NR (NR)	Final=3221.8 (3094.9, 3348.8)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Hollis et al., 2011	RCT/CCT	Y	ND	ND	N	ND	N	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Holvik et al., 2013	Prospective Cohort	51–70 years; age 65–79 years; home-dwelling	Not specified	Norwegian Epidemiologic Osteoporosis Studies (NOREPOS)	Government	Norway	21774/1022/72	71.9 (3.9)/NR		Other; 46.1–59.2% good or very good health	median (25th and 75th percentiles) s-25(OH)D in the randomly sampled subcohort was 53.5 (42.2, 67.8) nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Holvik et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Gender; Anthropometrics- BMI; Sun Exposure- Month Of Blood Sample	Primary-Hip Fracture	25(OH)D	Q1: 4.5–42.1	10.7 yrs	317/256	adjusted/HR	1.34	1.05, 1.70	
					25(OH)D	Q2: 42.2–53.5	10.7 yrs	294/255	adjusted/HR	1.13	0.90, 1.44	
					25(OH)D	Q3: 53.5–67.8	10.7 yrs	272/255	adjusted/HR	1.1	0.87, 1.39	
					25(OH)D	Q4: 67.9–250.0	10.7 yrs	279/256	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Holvik et al., 2013	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Hosseinpanah et al., 2011	Nested Case Control	19–50 years; 51–70 years; Healthy; free of CVD and kidney disease; age >30	Not specified	Tehran Lipid and Glucose Study (TLGS)	Unclear	Tehran, Iran	502/502/48.6	56.84 (11.17)/NR			25-OH-D concentration (ng/ml): cases- 12.5 (8.4-24.4); controls 18.1(11–31)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Hosseinpanah et al., 2011	Nested Case Control	age, sex, month of study entry, length of follow up	Anthropometrics- BMI; Medical Conditions- Diabetes Mellitus, Hypertension, Hypercholesterolemia, Hypertriglyceridemia, Low HDL	Primary- Cardiovascular Disease	25(OH)D	<10 ng/mL	5.7 yrs	85/133	Adjusted/OR	2.9	1.76, 4.67	<0.001
					25(OH)D	10–14.99 ng/mL	5.7 yrs	86/173	Adjusted/OR	1.46	0.83, 2.56	0.18
					25(OH)D	>=15ng/mL	5.7 yrs	80/196	Adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Hosseinpanah et al., 2011	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	**Justification of Final Adjusted Model Selection?**	**Clear Definition of Outcome Including Time of Ascertainment?**	**Loss to Followup <20%?**	**Do the Authors Specify a Primary Outcome?**	**Prospective Collection of Data?**	**Analysis Was Planned When Cohort Was Formed?**	**Justification of Sample Size (Includes Sample Size Calculations)?**	**Overall Grade**	**Explanation for Grade (if Not A)**
Y	N	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from C to B

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Houston et al., 2012	Prospective Cohort	70–79 years; black and white; no difficulty walking 1/4 mile, up 10 steps, or performing basic ADLs; free of life-threatening illness	lacked 25(OH)D measurements; missing data on pertinent covariates; lacked follow-up visits at year 4 or 6	Health, Aging and Body Composition	Government	USA; Pittsburgh, Memphis	2307/1971/51.1	74.7 (2.9)/NR	Non-Hispanic White=615; Non-Hispanic Black=385	Other; diabetes, cvd, copd, knee pain	1/3- 25(OH)D <50nmol/L, 2/3–<75nmol/L

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Houston et al., 2012	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Multivitamin And Vitamin D-Containing Supplement Use; Demographics (Age, Sex, Race/Ethnicity)- Age, Gender, Race, education; Anthropometrics- BMI; Medical Conditions- Kidney Function, Cognitive Function, Depressive Symptoms, Diabetes Mellitus, Cardiovascular Disease, Chronic Obstructive Pulmonary Disease, Knee Pain; Sun Exposure- Season; Smoking, Other Lifestyle Factors- Smoking Status, Alcohol Consumption, Physical Activity; Other - Prior Hospitalization	Secondary-Knee Extensor Strength	25(OH)D <50 nmol/L		1818	12.83 (SE=0.27)	Final=11.9 (SE=0.2)	NC (NC)	0.76
					25(OH)D 50–<75 nmol/L			13.01 (SE=0.27)	Final=11.9 (SE=0.2)	NC (NC)	.
					25(OH)D >=75 nmol/L			12.91 (SE=0.27)	Final=11.8 (SE=0.2)	NC (NC)	.
				Secondary-Grip Strength	25(OH)D <50 nmol/L		1971	28.87 (SE=0.51)	Final=29.2 (SE=0.4)	NC (NC)	0.09
					25(OH)D 50–<75 nmol/L			29.71 (SE=0.50)	Final=29.8 (SE=0.4)	NC (NC)	.
					25(OH)D >=75 nmol/L			29.81 (SE=0.50)	Final=30.0 (SE=0.4)	NC (NC)	.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Houston et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	Y	N	B	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Hutchinson et al., 2010	Prospective Cohort	19–50 years; 51–70 years; 25–84	Not specified	Tromso	Government	Tromso, Norway	7161/7161/59.8	58.9 (10.2)/NR			Mean 25(OH)D level in the total non-smoking population -52.3 +/-16.5, men- 53.5+/-16.0 and women- 51.5 +/-16.8 nmol/l (P<0.001). Mean 25(OH)D level for smokers was 72.0G+/-0.1, men- 70.5+/-19.0 and women- 73.0+/-20.7 nmol/l (P=0.002).

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Hutchinson et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Gender; Anthropometrics- BMI; Medical Conditions- Hypertension, Prior Cvd, Diabetes, Prior Cancer; Smoking, Other Lifestyle Factors- Smoking; Other - Creatinine	Primary-All-Cause Death	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)-nonsmokers	11.7 yrs	247/1184	adjusted/HR	1.32	1.07–1.62	NR
					25(OH)D	Quartile 2: mean=46.7 (sd=6.0)-nonsmokers	11.7 yrs	198/1187	adjusted/HR	1.06	0.86–1.31	
					25(OH)D	Quartile 3: mean=56.2 (sd=6.4)-nonsmokers	11.7 yrs	190/1192	adjusted/HR	1.09	0.88–1.34	
					25(OH)D	Quartile 4: mean=72.3 (sd=13.2)-nonsmokers	11.7 yrs	163/1188	adjusted/HR	1	Reference	
					25(OH)D	Quartile 1: mean=33.8 (sd=7.6)-smokers	11.7 yrs	156/597	adjusted/HR	1.06	0.83–1.35	NR
					25(OH)D	Quartile 2: mean=46.7 (sd=6.0)-smokers	11.7 yrs	143/606	adjusted/HR	0.97	0.76–1.25	
					25(OH)D	Quartile 3: mean=56.2 (sd=6.4)-smokers	11.7 yrs	138/607	adjusted/HR	1.04	0.81–1.33	
					25(OH)D	Quartile 4: mean=72.3 (sd=13.2)-smokers	11.7 yrs	124/600	adjusted/HR	1	Reference	
				Primary-Cvd Mortality	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)-nonsmokers	11.7 yrs	106/1184	adjusted/HR	1.08	0.79–1.48	NR
					25(OH)D	Quartile 2: mean=46.7 (sd=6.0)-nonsmokers	11.7 yrs	81/1187	adjusted/HR	0.84	0.61–1.15	
					25(OH)D	Quartile 3: mean=56.2 (sd=6.4)-nonsmokers	11.7 yrs	62/1192	adjusted/HR	0.71	0.51–1.01	
					25(OH)D	Quartile 4: mean=72.3 (sd=13.2)-nonsmokers	11.7 yrs	76/1188	adjusted/HR	1	Reference	
					25(OH)D	Quartile 1: mean=33.8 (sd=7.6)-smokers	11.7 yrs	45/597	adjusted/HR	0.93	0.61–1.44	NR
					25(OH)D	Quartile 2: mean=46.7 (sd=6.0)-smokers	11.7 yrs	57/606	adjusted/HR	1.1	0.73–1.67	
					25(OH)D	Quartile 3: mean=56.2 (sd=6.4)-smokers	11.7 yrs	46/607	adjusted/HR	1.04	0.67–1.60	
					25(OH)D	Quartile 4: mean=72.3 (sd=13.2)-smokers	11.7 yrs	40/600	adjusted/HR	1	Reference	
				Primary-Cancer Mortality	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)-nonsmokers	11.7 yrs	72/1184	adjusted/HR	1.14	0.80–1.63	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	Quartile 2: mean=46.7 (sd=6.0)-nonsmokers	11.7 yrs	69/1187	adjusted/HR	1.13	0.80–1.61	
					25(OH)D	Quartile 3: mean=56.2 (sd=6.4)-nonsmokers	11.7 yrs	74/1192	adjusted/HR	1.23	0.87–1.75	
					25(OH)D	Quartile 4: mean=72.3 (sd=13.2)-nonsmokers	11.7 yrs	58/1188	adjusted/HR	1	Reference	
					25(OH)D	Quartile 1: mean=33.8 (sd=7.6)-smokers	11.7 yrs	55/597	adjusted/HR	0.82	0.56–1.21	NR
					25(OH)D	Quartile 2: mean=46.7 (sd=6.0)-smokers	11.7 yrs	54/606	adjusted/HR	0.86	0.59–1.26	
					25(OH)D	Quartile 3: mean=56.2 (sd=6.4)-smokers	11.7 yrs	60/607	adjusted/HR	1.02	0.70–1.48	
					25(OH)D	Quartile 4: mean=72.3 (sd=13.2)-smokers	11.7 yrs	56/600	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Hutchinson et al., 2010	N	Y	N	Y						N

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Islam et al., 2010	RCT/CCT	9–18 years; 19–50 years; 18–36 years; no history of serious medical conditions; residing in the city for at least 2 years; no history of medication known to affect bone metabolism	Not specified		Manufacturer	Dhaka, Bangladesh	200/116/100	22.9 (3.9)/NR			placebo-35.0 +/-9.4 nmol/L Vit D-37.1+/-12.1 nmol/L VitD+Ca- 37.8+/-10.9 nmol/L MMN+D+Ca- 36.9+/-12.5 nmol/L

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Islam et al., 2010	RCT/CCT	NR	NR	Secondary-Femoral Neck BMC	D VD (Vit D 10 µg)/day		40	3.384 (sd=0.660)	change=0.061 (sd=0.205)	+0.14 (0.05, 0.22)	.
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	3.436 (sd=0.551)	change=0.069 (sd=0.174)	+0.14 (0.07, 0.22)	.
					D Placebo		35	3.316 (sd=0.533)	change=-0.075 (sd=0.146)		.
				Secondary-Femoral Neck BMD	D VD (Vit D 10 µg)/day		40	0.8 (sd=0.118)	change=0.012 (sd=0.028)	+0.02 (0.01, 0.03)	.
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	0.799 (sd=0.120)	change=0.013 (sd=0.030)	+0.02 (0.01, 0.03)	.
					D Placebo		35	0.768 (sd=0.967)	change=-0.010 (sd=0.012)		.
				Secondary-Lumbar Spine L2-L4 BMC	D VD (Vit D 10 µg)/day		40	32.548 (sd=4.845)	change=0.620 (sd=2.442)	+0.58 (-0.84, 2.00)	0.42
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	31.782 (sd=5.469)	change=0.687 (sd=2.761)	+0.65 (-0.82, 2.12)	0.39
					D Placebo		35	32.399 (sd=4.853)	change=0.042 (sd=3.673)		.
				Secondary-Lumbar Spine L2-L4 BMD	D VD (Vit D 10 µg)/day		40	0.898 (sd=0.113)	change=0.013 (sd=0.036)	+0.02 (-0, 0.04)	0.12
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	0.895 (sd=0.138)	change=0.010 (sd=0.042)	+0.01 (-0.01, 0.03)	0.22
					D Placebo		35	0.891 (sd=0.101)	change=-0.003 (sd=0.049)		.
				Secondary-Trochanter BMC	D VD (Vit D 10 µg)/day		40	5.818 (sd=1.289)	change=0.158 (sd=0.549)	+0.31 (0.09, 0.53)	0.01
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	5.877 (sd=1.335)	change=0.090 (sd=0.419)	+0.24 (0.06, 0.43)	0.01
					D Placebo		35	5.885 (sd=1.125)	change=-0.151 (sd=0.389)		.
				Secondary-Trochanter BMD	D VD (Vit D 10 µg)/day		40	0.634 (sd=0.097)	change=0.002 (sd=0.021)	+0.02 (0.01, 0.03)	0.002
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	0.625 (sd=0.105)	change=0.001 (sd=0.026)	+0.02 (0.01, 0.03)	0.01
					D Placebo		35	0.619 (sd=0.082)	change=-0.017 (sd=0.029)		.
				Secondary-Ward's Triangle BMD	D VD (Vit D 10 µg)/day		40	0.654 (sd=0.131)	change=0.010 (sd=0.035)	+0.03 (0.01, 0.04)	.

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
					D VD-Ca (Vit D 10 µg + calcium 600 mg)/day		41	0.654 (sd=0.132)	change=0.015 (sd=0.031)	+0.03 (0.02, 0.05)	.
					D Placebo		35	0.628 (sd=0.108)	change=-0.018 (sd=0.027)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Islam et al., 2010	RCT/CCT	Y	ND	ND	Y	Y	ND	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Jackson et al., 2011	RCT/CCT	19–50 years; 51–70 years; Postmenopausal women; 50–79 years; not likely to change residence; no evidence of a medical condition associated with predicted survival of less than 3 years at the time of enrollment	Not specified	WHI	Government	USA; multiple	1970/1528/100	NR/NR	Non-Hispanic White=828; Hispanic=42; Non-Hispanic Black=119; Asian=0; Race_other1=08; Race_other2=03	Post menopausal	vitamin D intake: placebo- 7.54+/-6.36 ug/d, CaD- 7.42+/-5.84 ug/d calcium intake: placebo- 1049+/-625.7 mg/d, CaD- 1,039+/-635.1 mg/d

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Jackson et al., 2011	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Ethnicity, Height; Other - Whole-Body Bone Area, Percent Lean Mass, Physical Activity, Baseline Hormone Use And Hormone Therapy Trial Randomization (Final Model Nr)	Secondary-Intertrochanteric BMD	D3 (400 IU Vit D3+1000 mg elemental calcium)/day		777	0.746 (sd=0.136)	final=0.749 (sd=0.135)	+0.02 (0.01, 0.04)	.
					D3 placebo		751	0.725 (sd=0.134)	final=0.725 (sd=0.137)		.
				Secondary-Narrow Neck BMD	D3 (400 IU Vit D3+1000 mg elemental calcium)/day		777	0.736 (sd=0.129)	final=0.742 (sd=0.133)	+0.02 (0.01, 0.03)	0.003
					D3 placebo		751	0.723 (sd=0.131)	final=0.722 (sd=0.136)		.
				Secondary-Shaft BMD	D3 (400 IU Vit D3+1000 mg elemental calcium)/day		777	1.18 (sd=0.181)	final=1.199 (sd=0.189)	+0.03 (0.01, 0.05)	.
					D3 placebo		751	1.155 (sd=0.181)	final=1.165 (sd=0.190)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Jackson et al., 2011	RCT/CCT	Y	Y	Y	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Jacobs et al., 2011	Nested Case Control	breast cancer survivors who had completed primary treatment of early stage breast cancer within the previous 4 y.		Women's Healthy Eating and Living (WHEL)	Government	USA; multiple	1024/500/100	51.9 (9.0)/NR	Non-Hispanic White=857; Hispanic=53; Non-Hispanic Black=29	Cancer in remission	All: deficient (<10ng/ml) 51, insufficient (>/=10, <20) 282, suboptimal (>/= 20, <30) 410, optimal (>/= 30) 281

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Jacobs et al., 2011	Nested Case Control	clinical site, cancer stage, age at cancer diagnosis, date of random assignment into the WHEL Study, and date of original cancer diagnosis	NR	Primary-Mortality	25(OH)D	Insufficient, <20 ng/ml	7.3 yrs	nr/164	adjusted/OR	1.13	0.72, 1.79	0.59
					25(OH)D	Sufficient, =20 ng/ml	7.3 yrs	nr/336	adjusted/OR	1	Reference	
				Primary-Breast Cancer	25(0H)D	<10ng/mL(deficient)	NR	nr/51	adjusted/OR	1.14	0.57, 2.31	
					25(0H)D	>=10 and <20ng/mL(insufficient)	NR	nr/282	adjusted/OR	1	0.68, 1.48	
					25(0H)D	>=20 and <30ng/mL(suboptimal)	NR	nr/410	adjusted/OR	1.05	0.76, 1.47	
					25(0H)D	>=30ng/mL(optimal)	NR	nr/281	adjusted/OR	1	reference	0.850
					25(0H)D	<10ng/mL(deficient)-Premenopausal women	NR	nr/6	adjusted/OR	0.17	0.01, 4.56	
					25(0H)D	>=10 and <20ng/mL(insufficient)-Premenopausal women	NR	nr/31	adjusted/OR	1.02	0.33, 3.16	
					25(0H)D	>=20 and <30ng/mL(suboptimal)-Premenopausal women	NR	nr/45	adjusted/OR	1.76	0.64, 4.87	
					25(0H)D	>=30ng/mL(optimal)-Premenopausal women	NR	nr/36	adjusted/OR	1	reference	0.610
					25(0H)D	<10ng/mL-Postmenopausal women	NR	nr/37	adjusted/OR	1.45	0.62,3.37	
					25(0H)D	>=10 and <20ng/mL-Postmenopausal women	NR	nr/202	adjusted/OR	1.09	0.68, 1.76	
					25(0H)D	>=20 and <30ng/mL-Postmenopausal women	NR	nr/266	adjusted/OR	0.9	0.60, 1.36	
					25(0H)D	>=30ng/mL-Postmenopausal women	NR	nr/187	adjusted/OR	1	reference	0.490
				Primary-Lethal Breast Cancer	25(0H)D	<20ng/mL(insufficient)	NR	nr/164	adjusted/OR	1.13	0.72, 1.79	
					25(0H)D	>=20ng/mL(sufficient)	NR	nr/336	adjusted/OR	1	reference	0.590

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Jacobs et al., 2011	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jacobsen et al., 2012	Prospective Cohort	51–70 years; without prior history of ischemic heart disease	Not specified	Copenhagen City Heart Study	university and hospital fund	Copenhagen, Denmark	10170/10170/56	57 (49–66)/NR		Not Reported	25(OH)D level-44nmol/L(26–58)

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Jacobsen et al., 2012	Prospective Cohort	NA	Demographics (Age, Sex, Race/Ethnicity)- Sex, Age; Anthropometrics- BMI; Medical Conditions- Diabetes, Plasma Total Cholesterol, High-Density Lipoprotein Cholesterol, Systolic Blood Pressure, And Estimated Glomerular Filtration Rate; Sun Exposure- Month Of Blood Draw; Smoking, Other Lifestyle Factors- Physical Activity, Smoking, Alcohol Consumption	Primary-Nonfatal Ischemic Heart Disease	25(OH)D	<25.0 nmol/L	29 yrs	381/2553	Adjusted/HR	1.08	0.85, 1.37	0.1
					25(OH)D	25.0–49.9 nmol/L	29 yrs	648/4068	Adjusted/HR	1.01	0.81, 1.26	
					25(OH)D	50.0–74.9 nmol/L	29 yrs	391/2470	Adjusted/HR	0.91	0.72, 1.15	
					25(OH)D	>=75.0 nmol/L	29 yrs	158/1079	Adjusted/HR	1	Reference	
				Primary-Nonfatal MI	25(OH)D	<25.0 nmol/L	29 yrs	224/2553	Adjusted/HR	1.17	0.83, 1.63	0.4
					25(OH)D	25.0–49.9 nmol/L	29 yrs	350/4068	Adjusted/HR	0.97	0.71, 1.34	
					25(OH)D	50.0–74.9 nmol/L	29 yrs	228/2470	Adjusted/HR	1.02	0.74, 1.42	
					25(OH)D	>=75.0 nmol/L	29 yrs	89/1079	Adjusted/HR	1	Reference	
				Primary-Fatal Ischemic Heart Disease/MI	25(OH)D	<25.0 nmol/L	29 yrs	422/2553	Adjusted/HR	1.53	1.18, 1.98	<0.001
					25(OH)D	25.0–49.9 nmol/L	29 yrs	627/4068	Adjusted/HR	1.23	0.96, 1.58	
					25(OH)D	50.0–74.9 nmol/L	29 yrs	367/2470	Adjusted/HR	1.18	0.91, 1.54	
					25(OH)D	>=75.0 nmol/L	29 yrs	106/1079	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Jacobsen et al., 2012	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	Y	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from C to B

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jacobsen et al., 2013	Prospective Cohort	51–70 years; had 25(OH)D measurement	Not specified	Copenhagen City Heart Study	University and hospital fund	Copenhagen, Denmark	10170/10170/56	56 (48–65)/NR			25(OH)D level-44nmol/L(26–58)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Jacobsen et al., 2013	Prospective Cohort	NA	Demographics (Age, Sex, Race/Ethnicity)- Age, Gender; Anthropometrics- BMI; Medical Conditions- Hypertension, Diabetes Mellitus, Atrial Fibrillation, Use Of Antihypertensive Medication, Plasma Total Cholesterol, HDL Cholesterol, Estimated Glomerular Filtration; Sun Exposure- Month Of Blood Draw; Smoking, Other Lifestyle Factors- Physical Activity, Smoking, Alcohol Consumption	Primary-Ischemic Stroke	25(OH)D	<25.0 nmol/L	29 yrs	350/2553	Adjusted/HR	1.36	1.09, 1.70	<0.001
					25(OH)D	25.0–49.9 nmol/L	29 yrs	504/4068	Adjusted/HR	1.1	0.89, 1.36	
					25(OH)D	50.0–74.9 nmol/L	29 yrs	277/2470	Adjusted/HR	0.92	0.74, 1.16	
					25(OH)D	>=75.0 nmol/L	29 yrs	125/1079	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Jacobsen et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	Y	N	A	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jassal et al., 2010	Prospective Cohort	Caucasian; middle-class; community dwelling adults; Not specified	lacked 25(OH)D, 1, 25(OH)2D and PTH measurements; eGFR < 15mL/min/1.73 m^2	Rancho Bernardo Study	Government	USA; San Diego, CA	1073/1073/62 %	74 (10)/NR	Non-Hispanic White=100	Not Reported	25(OH)D - 42(14) ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Jassal et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI, Medical Conditions - Prevalent Cardiovascular Disease; Medical Conditions- Prevalent Cvd; Smoking, Other Lifestyle Factors- Exercise, Sun Exposure, Season Of Blood Draw; Other - Systolic Blood Pressure, LDL Cholesterol, Fasting Glucose, Log (Urine Albumin/Creatinine Ratio), eGFR	Primary- Cardiovascular Mortality	25(OH)D	per SD increase in serum 25(OH)D	10.4 yrs	111/1073	Adjusted/HR	1.07	0.86, 1.33	NS
					1,25(OH)2D	per SD increase in log of serum 1,25(OH)2D	10.4 yrs	111/1073	Adjusted/HR	0.98	0.80, 1.21	NS

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Jassal et al., 2010	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	Y	A	should get ref 21 to verify eligibility criteria and sampling method --- Population a) sampling consecutive Outcome c) primary outcome changed to NA Grade changed from B to A

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Jenab et al., 2010	Nested Case Control	19–50 years; 51–70 years; geographic or administrative boundaries at each study center; age 25–82 (mostly 35–70)	anal cancer; missing matching information; missing laboratory 25-(OH) D data	EPIC	Government	Germany (specify city, if given);UK;Denmark, France, Greece, Italy, the Netherlands, Norway, Spain, Sweden	2496/2496/50.3	58.6 (7.2)/30.3–76.6		Not Reported	Circulating 25-(OH)D geometric mean (5th–95th percentile): colon cases- 51.7 nmol/L (24.1–104.4) controls- 57.2 nmol/L (28.0–114.8) rectal cases- 54.9 nmol/L (26.3–111.0) controls- 55.4 nmol/L (24.7–116.5)

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Jenab et al., 2010	Nested Case Control	age (plus or minus six months at recruitment), sex, study center, time of the day at blood collection, and fasting status at the time of blood collection (less than three hours, three to six hours, and more than six hours). Women were further matched by m	Other Nutrients Or Dietary Factors- Total Dietary Energy Consumption, Intake Of Total Fruits, Vegetables, Meat Or Meat Products; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Education; Anthropometrics- Body Mass Index; Sun Exposure- Season Of Blood Collection; Smoking, Other Lifestyle Factors- Smoking Status/Duration/Intensity, Total Physical Activity, Alcohol; Other - Time Of The Day At Blood Collection, Fasting Status At The Time Of Blood Collection, Menopausal Status, Phase Of Menstrual Cycle At Time Of Blood Collection, Usage Of Hormone Replacement Therapy At Time Of Blood Collection	Primary-Colorectal Cancer	25(0H)D	Quintile 1: <25nmol/l	NR	64/116	adjusted/HR	1.32	0.87, 2.01	NR
					25(0H)D	Quintile 2:>=25<50nmol/l	NR	473/873	adjusted/HR	1.28	1.05, 1.56	NR
					25(0H)D	Quintile 3:>=50<75nmol/l	NR	448/909	adjusted/HR	1	reference	NR
					25(0H)D	Quintile 4:>=75<100nmol/l	NR	173/382	adjusted/HR	0.88	0.68, 1.13	<0.001
					25(0H)D	Quintile 5:>=100nmol/l	NR	90/216	adjusted/HR	0.77	0.56, 1.06	<0.001
				Primary-Colon Cancer	25(0H)D	Quintile 1:<25nmol/l	NR	45/72	adjusted/HR	1.9	1.10, 3.29	NR
					25(0H)D	Quintile 2:>=25<50nmol/l	NR	300/549	adjusted/HR	1.36	1.05, 1.76	NR
					25(0H)D	Quintile 3:>=50<75nmol/l	NR	286/581	adjusted/HR	1	reference	NR
					25(0H)D	Quintile 4:>=75<100nmol/l	NR	104/242	adjusted/HR	0.86	0.62, 1.17	<0.001
					25(0H)D	Quintile 5:>=100nmol/l	NR	50/126	adjusted/HR	0.71	0.46, 1.08	<0.001
				Primary-Rectum Cancer	25(0H)D	Quintile 1:<25nmol/l	NR	NR/NR	adjusted/HR	0.77	0.37, 1.59	NR
					25(0H)D	Quintile 2:>=25<50nmol/l	NR	NR/NR	adjusted/HR	1.17	0.84, 1.65	NR
					25(0H)D	Quintile 3:>=50<75nmol/l	NR	NR/NR	adjusted/HR	1	reference	NR
					25(0H)D	Quintile 4:>=75<100nmol/l	NR	NR/NR	adjusted/HR	0.93	0.60, 1.45	0.288
					25(0H)D	Quintile 5:>=100nmol/l	NR	NR/NR	adjusted/HR	0.82	0.48, 1.40	0.320

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Jenab et al., 2010	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	B	cases ascertained from cancer registries, not verified independently Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Johansson et al., 2012	Prospective Cohort	70–81 years; able to walk without aids; give signed informed consent; provide self-reported data	Not specified	MrOS	Unclear	Sweden: Gothenberg, Malmö, Uppsala	2878/2878/0	75.7/3.4		Other; some with diabetes, htn, cancer, stroke, MI, angina	<25 nmol/l - 20 (74); 25–49 nmol/l 373 (75); 50–74 nmol/l- 735(57); 75–99 nmol/l- 317(42); =100 nmol/l- 106(34)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Johansson et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Current Age; Medical Conditions- Past History Of Cancer, Angina, Diabetes; Smoking, Other Lifestyle Factors- Outdoor Activity, Physical Activity Walking; Other - Current Time Since Baseline, Total Hip BMD, General Health	Primary-Death	25(OH)D	per SD decrease	8.2 yrs	577/2878	adjusted/HR	1.16	1.06, 1.26	NR

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Johansson et al., 2012	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Johnson et al., 2012	RCT/CCT	Postmenopausal women; Postmenopausal women; 50–79 years of age	previous history of breast cancer, history of other cancers within the previous 10 years, medical conditions likely to result in death within 3 years, conditions likely to interfere with retention in the study	WHI Mammogram Density Ancillary Study	Government	USA	492/330/100	62 (8)/NR	Non-Hispanic White=48; Hispanic=12; Non-Hispanic Black=36; Asian=4	Post menopausal	Table 1 (need to discuss what to enter)

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Johnson et al., 2012	RCT/CCT	NR	NR	Secondary-Percent Mammographic Density	D3 (Vit D3 400 IU+1,000 mg calcium)/day-overall		179	3.7 (2.9, 4.8)	final=3.6 (2.9, 4.6)	+0.8 (-0.2, 1.8)	0.1
					D3 placebo-overall		151	2.8 (2.1, 3.7)	final=2.8 (2.2, 3.7)		.
					D3 (Vit D3 400 IU+1,000 mg calcium)/day-Vit D intake at baseline < 200 IU/day		87	3.6 (2.5, 5.2)	final=3.5 (2.5, 4.9)	+0.5 (-0.9, 1.9)	0.47
					D3 placebo-Vit D intake at baseline < 200 IU/day		77	3 (2.1, 4.5)	final=3 (2.1, 4.3)		.
					D3 (Vit D3 400 IU+1,000 mg calcium)/day-Vit D intake at baseline >= 400 IU/day		53	4.3 (2.9, 6.4)	final=4 (2.6, 6.0)	+1.7 (-0.1, 3.5)	0.07
					D3 placebo-Vit D intake at baseline >= 400 IU/day		44	2.7 (1.5, 4.8)	final=2.3 (1.3, 4.2)		.
					D3 (Vit D3 400 IU+1,000 mg calcium)/day-Vit D intake at baseline 200 ~ 400 IU/day		29	2.4 (1.1, 5.3)	final=2.8 (1.4, 5.6)	-0.4 (-2.5, 1.7)	.
					D3 placebo-Vit D intake at baseline 200 ~ 400 IU/day		24	2.5 (1.3, 5.1)	final=3.2 (1.7, 6.1)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Johnson et al., 2012	RCT/CCT	Y	Y	N	N	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jones et al., 2012	Prospective Cohort	Pregnant or lactating women; Healthy; nonsmoking; healthy, uncomplicated term pregnancy; >=2 frozen CB serum samples in storage; allergic outcomes assessed at 12 months of age (offspring)	Not specified		Government	Australia;Perth	231/231/48.5 (neonatal)	33.4 (4.5)/NR	Non-Hispanic White=797; Asian=39; Race_other1= 26		The mean (SD) CB 25(OH)D3 = 58.4 (24.1) nmol/L, range= 9.18 to 246.34 nmol/l

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Jones et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Infant Gender, Maternal Age, Maternal Ethnicity; Sun Exposure- Season Of Birth	Primary-Eczema	25(OH)D3	per 10 nmol/L rise in CB 25(OH)D3	NR	78/231	adjusted/OR	0.857	0.739, 0.995	0.042

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Jones et al., 2012	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	Y	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jorde et al., 2010	RCT/CCT	19–50 years; 51–70 years; 21–70 years; BMI between 28.0–47.0 kg/m2; without a history of diabetes, coronary infarction, angina pectoris, stroke, renal stone disease, or sarcoidosis	Pregnant; lactating; women <50 years of age without adequate contraception; serum calcium>2.55 mmol/ L; males with serum creatinine >129 umol/ L; females with serum creatinine >104 umol/L		Manufacturer	Norway	438/330/64.2	47.5 (11.4)/NR		Overweight/obese; Other; using blood pressure or lipid lowering medication	58.0 ± 21.1 nmol/L

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Jorde et al., 2010	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Gender	Secondary-DBP	D3 DD (40,000 IU Vit D3/week)+500 mg calcium/day		114	76.5 (sd=9.8)	change=1.0 (sd=7.4)	+0.8 (-1.3, 2.9)	.
					D3 DP (20,000 IU Vit D3/week)+500 mg calcium/day		104	74.9 (sd=9.5)	change=1.0 (sd=8.3)	+0.8 (-1.4, 3.0)	.
					D3 PP (placebo)+500 mg calcium/day		112	74.8 (sd=10.0)	change=0.2 (sd=8.3)		.
				Secondary-SBP	D3 DD (40,000 IU Vit D3/week)+500 mg calcium/day		114	124 (sd=15)	change=1.2 (sd=11.4)	+2.3 (-0.9, 5.5)	.
					D3 DP (20,000 IU Vit D3/week)+500 mg calcium/day		104	121 (sd=13)	change=3.5 (sd=11.8)	+4.6 (1.3, 7.9)	.
					D3 PP (placebo)+500 mg calcium/day		112	125 (sd=16)	change=-1.1 (sd=12.8)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Jorde et al., 2010	RCT/CCT	ND	ND	ND	N	Y	Y	Y	Y	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Jorde et al., 2010	RCT/CCT	19–50 years; 51–70 years; 21–70 years; BMI 28.0–47.0 kg/m2	bisphosphonates; estrogen; h/o coronary infarction, angina; diabetes; stroke; renal stone disease; sarcoidosis; serum calcium > 2.55 mmol/L; males with serum creatinine > 129 µmol/L and females with serum creatinine > 104 µmol/L; using estrogen		Manufacturer	Norway	421/312/NR	50.8 (10.7)/NR		Overweight/obese	57.7 +/-20.7 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Jorde et al., 2010	RCT/CCT	NR	NR	Secondary-BMD L2-L4	D3 DD (Vit D3 40,000 IU/week+500 mg calcium)		110	1.27 (sd=0.155)	change=0.008 (sd=0.036)	+0.00 (-0.01, 0.01)	.
					D3 DP (Vit D3 20,000 IU/week+500 mg calcium)		97	1.235 (sd=0.161)	change=0.008 (sd=0.039)	+0.01 (0.0, 0.01)	.
					D3 PP (Placebo+500 mg calcium)		105	1.251 (sd=0.170)	change=0.007 (sd=0.042)		.
				Secondary-BMD Total Hip	D3 DD (Vit D3 40,000 IU/week+500 mg calcium)		110	1.107 (sd=0.133)	change=0.008 (sd=0.014)	-0.00 (-0.01, 0.0)	.
					D3 DP (Vit D3 20,000 IU/week+500 mg calcium)		97	1.067 (sd=0.128)	change=0.011 (sd=0.014)	+0.0 (-0.0, 0.01)	.
					D3 PP (Placebo+500 mg calcium)		105	1.092 (sd=0.130)	change=0.009 (sd=0.017)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Jorde et al., 2010	RCT/CCT	ND	ND	ND	N	Y	Y	Y	Y	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Kalra et al., 2012	RCT/CCT	Pregnant or lactating women; between 12–24 weeks gestation	Not specified		Government	Lucknow, India	299/71/100	26.7 (4.0)/NR			Group 1–31.7 nmol/L (IQR 14.0–57.2) Group 2- 32.0 nmol/L (IQR 14.5–45.7)

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Kalra et al., 2012	RCT/CCT	NR	NR	Secondary-Birth Weight	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		35	NR (NR)	Final=3.03 (1.71, 4.35)	-0.05 (-1.92, 1.82)	0.96
					1500 mg cholecalciferol (one dose 2nd trimester)		36	NR (NR)	Final=3.08 (1.71, 4.45)		.
				Secondary-Weight At 3 Mo	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		33	NR (NR)	Final=5.9 (5.8, 6.0)	+0 (-0.1, 0.1)	1
					1500 mg cholecalciferol (one dose 2nd trimester)		31	NR (NR)	Final=5.9 (5.8, 6.0)		.
				Secondary-Weight At 6 Mo	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		24	NR (NR)	Final=7.3 (7.1, 7.5)	+0.1 (-0.1, 0.3)	0.37
					1500 mg cholecalciferol (one dose 2nd trimester)		28	NR (NR)	Final=7.2 (7.0, 7.4)		.
				Secondary-Weight At 9 Mo	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		18	NR (NR)	Final=8.5 (8.3, 8.7)	+0.1 (-0.3, 0.5)	0.58
					1500 mg cholecalciferol (one dose 2nd trimester)		22	NR (NR)	Final=8.4 (8.1, 8.7)		.
				Secondary-Length At Birth	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		35	NR (NR)	Final=50.1 (49.8, 50.4)	-0.2 (-0.6, 0.2)	0.35
					1500 mg cholecalciferol (one dose 2nd trimester)		36	NR (NR)	Final=50.3 (50.0, 50.6)		.
				Secondary-Length At 3 Mo	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		33	NR (NR)	Final=59.9 (59.5, 60.3)	+0.1 (-0.6, 0.8)	0.79
					1500 mg cholecalciferol (one dose 2nd trimester)		31	NR (NR)	Final=59.8 (59.2, 60.4)		.

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
				Secondary-Length At 6 Mo	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		24	NR (NR)	Final=64.9 (64.0, 65.8)	+0.6 (-0.5, 1.7)	0.28
					1500 mg cholecalciferol (one dose 2nd trimester)		28	NR (NR)	Final=64.3 (63.6, 65.0)		.
				Secondary-Length At 9 Mo	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)		18	NR (NR)	Final=69.9 (69.2, 70.6)	+0.6 (-0.5, 1.7)	0.27
					1500 mg cholecalciferol (one dose 2nd trimester)		22	NR (NR)	Final=69.3 (68.5, 70.1)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Kalra et al., 2012	RCT/CCT	Y	ND	Y	N	ND	ND	ND	ND	Y	C	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Karakas et al., 2013	Prospective Cohort	Healthy; middle-aged	missing values; self-reported prevalent CHD; missing blood samples	MONICA/KORA Augsburg case-cohort study	Government	Germany (specify city, if given)	1783/964/24.5	51.9 (0.42)/35–74			male cases- 37.7(1.03), non-cases 43.9(1.02)\ female cases- 31.9(1.05), non-cases 39.7(1.01)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Karakas et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Sun Exposure- Season Of Blood Sampling; Other - Traditional Cardiovascular Risk Factors, CRP, Il-6, Sicam-1, Ip-10	Primary-Coronary Heart Disease	25(OH)D in men	54.14–153.92 nmol/L	11 yrs	225/964	Adjusted/HR	0.84	0.52, 1.35	0.461
					25(OH)D in men	35.05–54.13 nmol/L	11 yrs		Adjusted/HR	0.66	0.43, 1.02	
					25(OH)D in men	5.08–35.02 nmol/L	11 yrs		Adjusted/HR	1	Reference	
					25(OH)D in women	47.70–127.69 nmol/L	11 yrs	73/819	Adjusted/HR	0.42	0.19, 0.93	0.028
					25(OH)D in women	33.16–47.69 nmol/L	11 yrs		Adjusted/HR	0.67	0.35, 1.29	
					25(OH)D in women	9.87–33.15 nmol/L	11 yrs		Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Karakas et al., 2013	N	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	A	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Karkkainen et al., 2010	RCT/CCT	age at a minimum of 65 years at the end of November 2002,; living in the Kuopio Province at the onset of the trial,; not belonging to the former OSTPRE bone densitometry sample.	Not specified	OSTPRE-FPS	Manufacturer	Finland; Kuopio	750/591/100	67.4 (1.9)/NR		Post menopausal	intervention- 50.1 (18.8) nmol/l control- 49.2 (17.7) nmol/l (p=0.544)

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Karkkainen et al., 2010	RCT/CCT	NR	NR	Secondary-Femoral Neck BMD	D3 Vit D 800 IU+calcium 1,000 mg		280	0.866 (sd=0.13)	final=0.848 (sd=0.13)	-0.002 (-0.02, 0.02)	.
					D3 control (neither supplementation nor placebo)		311	0.865 (sd=0.12)	final=0.850 (sd=0.12)		.
				Secondary-Lumbar Spine BMD	D3 Vit D 800 IU+calcium 1,000 mg		259	1.039 (sd=0.17)	final=1.047 (sd=0.17)	-0.013 (-0.041, 0.016)	.
					D3 control (neither supplementation nor placebo)		285	1.052 (sd=0.17)	final=1.060 (sd=0.17)		.
				Secondary-Total Body BMD	D3 Vit D 800 IU+calcium 1,000 mg		195	1.069 (sd=0.09)	final=1.078 (sd=0.10)	-0.003 (-0.02, 0.02)	.
					D3 control (neither supplementation nor placebo)		238	1.079 (sd=0.09)	final=1.081 (sd=0.10)		.
				Secondary-Total Proximal Femur BMD	D3 Vit D 800 IU+calcium 1,000 mg		280	0.948 (sd=0.14)	final=0.934 (sd=0.14)	-0.005 (-0.03, 0.02)	.
					D3 control (neither supplementation nor placebo)		310	0.953 (sd=0.13)	final=0.939 (sd=0.13)		.
				Secondary-Trochanter BMD	D3 Vit D 800 IU+calcium 1,000 mg		280	0.783 (sd=0.14)	final=0.779 (sd=0.13)	-0.01 (-0.03, 0.01)	.
					D3 control (neither supplementation nor placebo)		310	0.797 (sd=0.13)	final=0.790 (sd=0.13)		.
				Secondary-Ward's Triangle	D3 Vit D 800 IU+calcium 1,000 mg		280	0.67 (sd=0.15)	final=0.652 (sd=0.14)	-0.001 (-0.02, 0.02)	.
					D3 control (neither supplementation nor placebo)		310	0.672 (sd=0.13)	final=0.653 (sd=0.13)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Karkkainen et al., 2010	RCT/CCT	ND	ND	N	Y	N	Y	N	N	N	C	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Karkkainen et al., 2010	RCT/CCT	age at a minimum of 65 years at the end of November 2002,; living in Kuopio province area at the onset of the trial; not belonging to the former OSTPRE bone densitometry sample.; ambulatory women		OSTRE-FPS	Private	Finland; Kuopio	3139/3139/100	67.4 (1.9)/65–71			Mean 25(OH)D concentrations (nmol/L): intervention- 50.1 (18.8) ;control- 49.2 (17.7) (P = 0.544)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Karkkainen et al., 2010	RCT/CCT	NR	NR	Primary-No Falls	Vit D3; Ca	1g/daily & 800 IU/daily	3 y	754/1566	Crude/OR	1.05	0.91, 1.20	>0.05
					Placebo; Ca	Placebo	3 y	740/1573	Crude/OR	1	Reference	
				Primary-Falls (>=1)	Vit D3; Ca	1g/daily & 800 IU/daily	3 y	1109/1566	Crude/OR	1.13	0.97, 1.32	>0.05
					Placebo; Ca	Placebo	3 y	1073/1573	Crude/OR	1	Reference	
				Primary-No Fall Requiring Medical Attention (FRMA)	Vit D3; Ca	1g/daily & 800 IU/daily	3 y	1308/1566	Crude/OR	0.84	0.70, 1.01	>0.05
					Placebo; Ca	Placebo	3 y	1274/1573	Crude/OR	1	Reference	
				Primary-Falls Requiring Medical Attention (FRMA) (=1)	Vit D3; Ca	1g/daily & 800 IU/daily	3 y	1488/1566	Crude/OR	0.72	0.53, 0.97	0.03
					Placebo; Ca	Placebo	3 y	1466/1573	Crude/OR	1	Reference	

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Karkkainen et al., 2010	RCT/CCT	ND	ND	N	Y	N	Y	N	N	Y	C	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Kestenbaum et al., 2011	Prospective Cohort	51–70 years; >65 years; ambulatory	use of a wheelchair in the home; current treatment for cancer; institutionalization,; need for a proxy respondent to provide informed consent; plans to move from the area within 3 years	CHS	Government	USA; Forsyth County, NC, Sacramento county, CA, Washington County, MD, Pittsburgh, PA	2312/2312/58	73 (4)/NR	Non-Hispanic Black=4		25.2+/- _ 10.2 ng/ml (interquartile range: 17.8 to 31.5 ng/ml).

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Kestenbaum et al., 2011	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race, Education; Anthropometrics- BMI; Medical Conditions- Diabetes, Hypertension; Sun Exposure- Season Of The Year; Smoking, Other Lifestyle Factors- Smoking, Physical Activity; Other - Systolic Blood Pressure, Levels Of C-Reactive Protein, HDL Cholesterol, Calcium And Phosphorus, eGFR	Primary-All-Cause Mortality	25(OH)D	>30 ng/ml	14 yrs	329/681	adjusted/HR	1	reference	
					25(OH)D	15–30 ng/ml	14 yrs	668/1247	adjusted/HR	1.15	1.00, 1.33	
					25(OH)D	<15 ng/ml	14 yrs	229/384	adjusted/HR	1.29	1.05, 1.57	
					25(OH)D	continuous per 10 ng/ml	14 yrs	1226/2312	adjusted/HR	1.09	1.02, 1.17	0.012
				Primary-Cardiovascular Mortality	25(OH)D	Continuous per 10 ng/ml lower 25(OH)D	14 yrs	389/2312	Adjusted/HR	1.06	0.94, 1.19	0.356
					25(OH)D	<15ng/ml	14 yrs	107/681	Adjusted/HR	1.17	0.83, 1.67	
					25(OH)D	15–30 ng/ml	14 yrs	207/1247	Adjusted/HR	1.01	0.78, 1.30	
					25(OH)D	>30 ng/ml	14 yrs	75/384	Adjusted/HR	1	Reference	
				Primary-Incident Heart Failure	25(OH)D	Continuous per 10 ng/ml lower 25(OH)D	14 yrs	504/2312	Adjusted/HR	0.95	0.86, 1.05	0.303
					25(OH)D	<15ng/ml	14 yrs	107/681	Adjusted/HR	1.17	0.83, 1.67	
					25(OH)D	15–30 ng/ml	14 yrs	207/1247	Adjusted/HR	1.01	0.78, 1.30	
					25(OH)D	>30 ng/ml	14 yrs	75/384	Adjusted/HR	1	Reference	
				Primary-Incident Myocardial Infarction	25(OH)D	Continuous per 10 ng/ml lower 25(OH)D	14 yrs	299/2312	Adjusted/HR	1.25	1.08, 1.44	0.002
					25(OH)D	<15ng/ml	14 yrs	88/681	Adjusted/HR	1.4	0.93, 2.12	
					25(OH)D	15–30 ng/ml	14 yrs	161/1247	Adjusted/HR	1.2	0.90, 1.59	
					25(OH)D	>30 ng/ml	14 yrs	50/384	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Kestenbaum et al., 2011	Y	Y	N	N						

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	Y	N	B	Population a) sampling consecutive Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Khadilkar et al., 2010	RCT/CCT	9–18 years; postmenarcheal; 14–15 years; attending a state run school from Feb 2006-April 2007	Not specified		Unclear	Pune, India	50/49/100	14.6/14.3–15.3		Not Reported	Vit D + Ca- 24.5 nmol/L (12.7–33.2) Placebo +Ca- 20.8 nmol/L (12.7–30.4)

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Khadilkar et al., 2010	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Height, Weight; Other - Calcium Compliance, Baseline Value Of Dietary Calcium Intake	Secondary-L2-L4 Bone Mineral Apparent Density	D2 Vit D2 300,000 IU x 4 times/year + 250 mg elemental calcium/day-overall		25	NR (NR)	change=4.2 (0.6, 9.3)	+0.5 (NC)	.
					D2 Placebo x 4 times/year + 250 mg elemental calcium/day-overall		24	NR (NR)	change=3.7 (1.0, 7.7)		.
				Secondary-L2-L4 BMC	D2 Vit D2 300,000 IU x 4 times/year + 250 mg elemental calcium/day-overall		25	NR (NR)	change=10.5 (4.6, 17.2)	-0.8 (NC)	.
					D2 Placebo x 4 times/year + 250 mg elemental calcium/day-overall		24	NR (NR)	change=11.3 (5.4, 18.0)		.
				Secondary-Total BMC	D2 Vit D2 300,000 IU x 4 times/year + 250 mg elemental calcium/day-overall		25	NR (NR)	change=10.1 (6.1, 14.7)	+1.9 (NC)	.
					D2 Placebo x 4 times/year + 250 mg elemental calcium/day-overall		24	NR (NR)	change=8.2 (4.9, 12.6)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Khadilkar et al., 2010	RCT/CCT	ND	ND	ND	Y	Y	ND	Y	Y	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Kilkkinen et al., 2009	Prospective Cohort	30 years or more	Current cardiovascular disease; lacking serum sample for 25(OH)D analysis	Mini-Finland Health Survey	Government	Finland;40 areas	6219/6219/54.7	49.4 (13.6)/NR			43.4 +/-19.7 nmol/L

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Kilkkinen et al., 2009	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Marital Status, Education; Anthropometrics- BMI; Medical Conditions- Diabetes, Blood Pressure; Smoking, Other Lifestyle Factors- Smoking, Physical Activity, Alcohol Consumption, HDL and LDL Cholesterol	Primary-Cardiovascular Death	25(OH)D	M:62–180 nmol/l |F:56.0–151.0 nmol/l	27.1 yrs (median)	150/1253	Adjusted/HR	0.76	0.61, 0.95	0.005
					25(OH)D	M:48.0–61.0 nmol/l |F:44.0–55.0 nmol/l	27.1 yrs (median)	171/1222	Adjusted/HR	0.86	0.70, 1.06	
					25(OH)D	M:38.0–47.0 nmol/l |F:34.0–43.0 nmol/l	27.1 yrs (median)	164/1284	Adjusted/HR	0.81	0.66, 1.00	
					25(OH)D	M:29.0–37.0 nmol/l |F:26.0–33.0 nmol/l	27.1 yrs (median)	194/1202	Adjusted/HR	1.04	0.86, 1.26	
					25(OH)D	M:5.0–28.0 nmol/l |F:4.0–25.0 nmol/l	27.1 yrs (median)	254/1258	Adjusted/HR	1	Reference	
				Primary-Cerebrovascular Death	25(OH)D	M:62–180 nmol/l |F:56.0–151.0 nmol/l	27.1 yrs (median)	33/1253	Adjusted/HR	0.48	0.31, 0.75	0.002
					25(OH)D	M:48.0–61.0 nmol/l |F:44.0–55.0 nmol/l	27.1 yrs (median)	48/1222	Adjusted/HR	0.69	0.48, 1.00	
					25(OH)D	M:38.0–47.0 nmol/l |F:34.0–43.0 nmol/l	27.1 yrs (median)	68/1284	Adjusted/HR	0.97	0.70, 1.35	
					25(OH)D	M:29.0–37.0 nmol/l |F:26.0–33.0 nmol/l	27.1 yrs (median)	52/1202	Adjusted/HR	0.8	0.57, 1.14	
					25(OH)D	M:5.0–28.0 nmol/l |F:4.0–25.0 nmol/l	27.1 yrs (median)	92/1258	Adjusted/HR	1	Reference	
				Primary-Coronary Disease Death	25(OH)D	M:62–180 nmol/l |F:56.0–151.0 nmol/l	27.1 yrs (median)	117/1253	Adjusted/HR	0.91	0.70, 1.18	0.2
					25(OH)D	M:48.0–61.0 nmol/l |F:44.0–55.0 nmol/l	27.1 yrs (median)	123/1222	Adjusted/HR	0.95	0.74, 1.22	
					25(OH)D	M:38.0–47.0 nmol/l |F:34.0–43.0 nmol/l	27.1 yrs (median)	96/1284	Adjusted/HR	0.73	0.56, 0.95	
					25(OH)D	M:29.0–37.0 nmol/l |F:26.0–33.0 nmol/l	27.1 yrs (median)	142/1202	Adjusted/HR	1.17	0.93, 1.48	
					25(OH)D	M:5.0–28.0 nmol/l |F:4.0–25.0 nmol/l	27.1 yrs (median)	162/1258	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Kilkkinen et al., 2009	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Kritchevsky et al., 2012	Prospective Cohort	70–79; community dwelling; black and white; no difficulty walking 0.25 miles, climbing 10 steps and performing basic ADLs; not enrolled in lifestyle intervention trials	PTH >250 pg/ml; 25(OH)D >75.25 pg/ml	Health ABC	Government	USA; Pittsburgh, Memphis	3075/2638/51.2	74.7 (2.9)/NR	Non-Hispanic White=61; Non-Hispanic Black=39	Other; well-functioning	serum 25(OH)D: 25.8 (10.3) ng/ml

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Kritchevsky et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Gender, Race, Education; Anthropometrics- BMI; Medical Conditions- Prevalent Diabetes, Hypertension, CVD, Cancer, Lung Disease; Sun Exposure- Season; Smoking, Other Lifestyle Factors- Smoking Status, Pack-Years, Alcohol Consumption, Time Walking, Usual 20-M Walking Speed; Other - Cognition, Depressive Symptoms, Cholesterol, PTH	Primary-All-Cause Mortality	25(OH)D	< 10 ng/ml	8.5 yrs	44/108	adjusted/HR	2.27	1.59, 3.24	<0.001
					25(OH)D	10 to <20 ng/ml	8.5 yrs	241/750	adjusted/HR	1.48	1.20, 1.84	
					25(OH)D	20 to <30 ng/ml	8.5 yrs	229/931	adjusted/HR	1.25	1.02, 1.52	
					25(OH)D	>=30 ng/ml	8.5 yrs	177/849	adjusted/HR	1	Reference	
					25(OH)D	< 10 ng/ml-whites	8.5 yrs	10/25	adjusted/HR	2.02	1.02, 3.99	0.001
					25(OH)D	10 to <20 ng/ml-whites	8.5 yrs	82/279	adjusted/HR	1.54	1.16, 2.06	
					25(OH)D	20 to <30 ng/ml-whites	8.5 yrs	138/620	adjusted/HR	1.22	0.96, 1.55	
					25(OH)D	>=30 ng/ml-whites	8.5 yrs	143/691	adjusted/HR	1	Reference	
					25(OH)D	< 10 ng/ml-blacks	8.5 yrs	34/83	adjusted/HR	2.59	1.57, 4.26	<0.001
					25(OH)D	10 to <20 ng/ml-blacks	8.5 yrs	159/471	adjusted/HR	1.76	1.20, 2.57	
					25(OH)D	20 to <30 ng/ml-blacks	8.5 yrs	91/311	adjusted/HR	1.6	1.07, 2.39	
					25(OH)D	>=30 ng/ml-blacks	8.5 yrs	34/158	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Kritchevsky et al., 2012	Y	Y	N	N						

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Kuhn et al., 2013	Prospective Cohort	Not specified	MI or stroke; without complete follow-up information; missing 25(OH)D values; missing covariate data	EPIC-Germany	Government	Germany (specify city, if given);Heidelberg, Potsdam	3115/2132/NR	NR (NR)/NR		Not Reported	plasma 25(OH)D of the 2132 sub cohort- 47.2 +/- 18.3 nmol/l

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Kuhn et al., 2013	Prospective Cohort	NA	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI, Waist Circumference; Sun Exposure- Center; Smoking, Other Lifestyle Factors- Alcohol Intake, Smoking, Physical Activity	Primary-Myocardial Infarction	25(OH)D	Q4: median 66.5	7.6 yrs	118/533	adjusted/HR	1	Reference	0.19
					25(OH)D	Q3: median 50.5	7.6 yrs	117/533	adjusted/HR	0.95	0.70, 1.28	
					25(OH)D	Q2: median 40.4	7.6 yrs	158/533	adjusted/HR	1.24	0.93, 1.66	
					25(OH)D	Q1: median 28.9	7.6 yrs	166/533	adjusted/HR	1.43	1.07, 1.92	
				Primary-Stroke	25(OH)D	Q4: median 66.6	7.6 yrs	111/533	adjusted/HR	1	Reference	0.19
					25(OH)D	Q3: median 50.5	7.6 yrs	101/533	adjusted/HR	0.86	0.63, 1.17	
					25(OH)D	Q2: median 40.4	7.6 yrs	102/533	adjusted/HR	0.83	0.61, 1.12	
					25(OH)D	Q1: median 28.9	7.6 yrs	157/533	adjusted/HR	1.37	1.02, 1.84	
				Primary-Cvd As Composite Endpoint	25(OH)D	Q4: median 66.5	7.6 yrs	229/533	adjusted/HR	1	Reference	0.12
					25(OH)D	Q3: median 50.5	7.6 yrs	218/533	adjusted/HR	0.89	0.70, 1.14	
					25(OH)D	Q2: median 40.4	7.6 yrs	260/533	adjusted/HR	1.06	0.83, 1.35	
					25(OH)D	Q1: median 28.9	7.6 yrs	323/533	adjusted/HR	1.41	1.11, 1.79	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Kuhn et al., 2013	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	ref 25 might be helpful reconciled

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Kuhn et al., 2013	Nested Case Control	Varied by country: generally adults 40–65	Not specified	EPIC	Private Foundation	Multiple Countries	2,782/2782/100	50.7 (8.8)/NR			reported in quartiles

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Kuhn et al., 2013	Nested Case Control	study center, age±3 months, menopausal status, exogenous hormone use at blood donation, time of day of blood collection, fasting status, phase of cycle	Demographics (Age, Sex, Race/Ethnicity)- Educational Level; Anthropometrics- BMI; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Alcohol Consumption, Smoking, Physical Activity; Other - Number Of Full-Term Pregnancies, Breastfeeding	Primary-Breast Cancer	25(OH)D	Q1: <=39.3	4.1 yrs	342/688	adjusted/OR	1	reference	0.67
					25(OH)D	Q2: 39.4–50.9	4.1 yrs	357/707	adjusted/OR	1.03	0.83, 1.29	
					25(OH)D	Q3: 51.0–63.0	4.1 yrs	324/670	adjusted/OR	0.94	0.74, 1.19	
					25(OH)D	Q4: >63.0	4.1 yrs	368/717	adjusted/OR	1.07	0.85, 1.36	
					25(OH)D	log2 (continuous)	4.1 yrs	1391/2782	adjusted/OR	1.01	0.86, 1.19	0.86

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Kuhn et al., 2013	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	Y	N	A	Discussion of power was in original article and may not be relevant to this specific nested case control.

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Kukuljan et al., 2009	RCT/CCT	51–70 years; Healthy; men; community-dwelling; Caucasian	had taken calcium and/or vitamin D supplements; Osteoporosis; used medication known to affect bone metabolism; medical condition known to affect bone metabolism, any chronic condition that might limit their ability to be involved in the intervention; current smoking; chronic condition that might limit ability to be involved in the intervention; lactose intolerance		Private Foundation	Australia;Victoria	180/85/0	59.9 (7.4)/50–79	Non-Hispanic White=100		serum 25(OH)D 86.2 ± 35.9 nmol/l

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Kukuljan et al., 2009	RCT/CCT	NR	NR	Secondary-Step Test	Ca & Vit D3 fortified milk Ig & 800 IU daily		43	9.90 (SD=2.9)	final=11.4 (SD=3.00)	-6 (-2.0, 0.75)	0.38
					Control		42	10.30 (SD=2.8)	final=12.0 (SD=3.30)		.
				Secondary-Gait Speed	Ca & Vit D3 fortified milk Ig & 800 IU daily		43	2.84 (SD=0.96)	final=2.79 (SD=1.17)	+0.13 (-0,36, 0.62)	0.6
					Control		42	3.08 (SD=1.36)	final=2.66 (SD=1.12)		.
				Secondary-Sway, Eyes Open, On Floor	Ca & Vit D3 fortified milk Ig & 800 IU daily		43	294.00 (SD=282)	final=326 (SD=344)	+147 (32.4, 261.6)	0.01
					Control		42	320.00 (SD=366)	final=179 (SD=147)		.
				Secondary-Sway, Eyes Closed, On Floor	Ca & Vit D3 fortified milk Ig & 800 IU daily		43	364.00 (SD=318)	final=241 (SD=192)	-79 (-207, 49)	0.22
					Control		42	285.00 (SD=232)	final=320 (SD=373)		.
				Secondary-Sway, Eyes Open, On Foam	Ca & Vit D3 fortified milk Ig & 800 IU daily		43	737.00 (SD=762)	final=596 (SD=733)	+248 (9, 487)	0.04
					Control		42	597.00 (SD=532)	final=348 (SD=266)		.
				Secondary-Sway, Eyes Closed, On Foam	Ca & Vit D3 fortified milk Ig & 800 IU daily		43	1317.00 (SD=875)	final=1045 (SD=787)	-209 (-721, 303)	0.42
					Control		42	1437.00 (SD=1217)	final=1254 (SD=1489)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Kukuljan et al., 2009	RCT/CCT	ND	ND	Y	Y	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Kukuljan et al., 2011	RCT/CCT	19–50 years; 51–70 years; Healthy; male; normal to below average BMD; community dwelling; Caucasian	use of calcium-vitamin D supplementation within the past 12 months; Prior fragility fracture; chronic condition that might limit participation in the trials; participation in resistance training; BMI >35kg/m2; lactose intolerance; any medical conditions or medication use known to affect bone metabolism; current smoker		Manufacturer	Australia; Geelong	180/89/0	59.9 (7.4)/NR	Non-Hispanic White=100		calcium intake: 911–1064 mg/d Serum vitamin D level: 34.5+/-14.4 ng/ml

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Kukuljan et al., 2011	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Changes In Weight	Secondary-L1-L3 Total Volumetric BMD	D3 fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D3)		45	164 (sd=25)	change=-0.6 (-2.1, 0.8)	-0.6 (-2.7, 1.6)	.
					D3 controls		44	171 (sd=34)	change=-0.05 (-1.5, 1.4)		.
				Secondary-L1-L3 Trabecular Volumetric BMD	D3 fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D3)		45	115 (sd=22)	change=-1.5 (-3.1, 0.9)	-2.3 (-6.4, 1.8)	.
					D3 controls		44	120 (sd=34)	change=0.8 (-2.9, 1.2)		.
				Secondary-Mid-Femur Cortical Volumetric BMD	D3 fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D3)		45	1104 (sd=39)	change=-1.0 (-1.4, -0.6)	-0.3 (-1.0, 0.4)	.
					D3 controls		44	1108 (sd=38)	change=-0.7 (-1.3, -0.2)		.
				Secondary-Mid-Tibia Cortical Volumetric BMD	D3 fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D3)		45	1105 (sd=43)	change=-1.2 (-1.7, -0.7)	-0.1 (-0.8, 0.6)	.
					D3 controls		44	1113 (sd=49)	change=-1.1 (-1.6, -0.5)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Kukuljan et al., 2011	RCT/CCT	Y	ND	Y	Y	ND	Y	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Laaksi et al., 2010	RCT/CCT	19–50 years; 18–28 years; no regular medication; passed the entry medical examination as healthy	use of supplementary vitamin D, multivitamins and cod liver oil		Government	Finland; Pori Brigade	164/328/0	NR/NR			Serum vitamin D level: intervention group- 78.7+/-™14.9 nmol/L placebo- 74.4™+/-20.8 nmol/L

Main Analyses (Dichotomous Outcomes)												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event / N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Laaksi et al., 2010	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Smoking	Primary-Self Reported Common Cold Symptoms	Vit D3	400 IU	6 months	45/80	Crude/OR	1.17	0.63, 2.16	0.619
					Placebo	Placebo	6 months	44/84	Crude/OR	1	reference	
				Primary-No Days Absent From Duty	Vit D3	400 IU	6 months	41/80	Crude/OR	1.89	1.01, 3.54	0.045
					Placebo	Placebo	6 months	30/84	Crude/OR	1	reference	

Main Analyses (Continuous Outcomes)											
Author,Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Laaksi et al., 2010	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Smoking	Secondary-Days Absent From Duty	Vit D3 400 IU		80	NR (NR)	final=2.2 (SD=3.2)	-0.8 (-1.9, 0.3)	0.096
					Placebo		84	NR (NR)	final=3.0 (SD=4.0)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Laaksi et al., 2010	RCT/CCT	Y	ND	Y	N	Y	Y	N	ND	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Lee et al., 2011	Nested Case Control	19–50 years; 51–70 years; U.S. male physicians; 40–84 years	vitamin A or beta carotene; cancer except non melanoma skin cancer; myocardial infarction, stroke, or transient ischemic attack; renal or liver disease; peptic ulcer; gout	Physicians' Health Study	Government	USA; multiple	618/618/0	NR/NR			NR

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Lee et al., 2011	Nested Case Control	NR	Other Nutrients Or Dietary Factors- Fasting Status, Dairy Calcium Intake; Demographics (Age, Sex, Race/Ethnicity)- Age, Race; Anthropometrics- BMI; Sun Exposure- Seasons; Smoking, Other Lifestyle Factors- Smoking Status, Vigorous Exercise	Primary-Colorectal Cancer	25(0H)D	Quartile 1 (median 15.7ng/mL)	NR	57/153	adjusted/OR	1	reference	
					25(0H)D	Quartile 2 (median 22.3ng/mL)	NR	41/138	adjusted/OR	0.71	0.42, 1.21	
					25(0H)D	Quartile 3(median 26.7ng/mL)	NR	74/173	adjusted/OR	1.24	0.76, 2.04	
					25(0H)D	Quartile 4(median 37.9ng/mL)	NR	57/154	adjusted/OR	1.08	0.62, 1.87	0.670
					1,25(OH)2D	Quartile 1 (median 25.5pg/mL)	NR	66/159	adjusted/OR	1	reference	
					1,25(OH)2D	Quartile 2 (median 31.2pg/mL)	NR	60/156	adjusted/OR	0.91	0.55, 1.50	
					1,25(OH)2D	Quartile 3(median 34.7pg/mL)	NR	53/149	adjusted/OR	0.84	0.51, 1.38	
					1,25(OH)2D	Quartile 4(median 41.1pg/mL)	NR	45/139	adjusted/OR	0.7	0.41, 1.18	0.240
				Primary-Colon Cancer	25(0H)D	Quartile 1 (median 15.7ng/mL)	NR	36/106	adjusted/OR	1	reference	
					25(0H)D	Quartile 2 (median 22.3ng/mL)	NR	37/109	adjusted/OR	0.95	0.52, 1.74	
					25(0H)D	Quartile 3 (median 26.7ng/mL)	NR	52/126	adjusted/OR	1.34	0.75, 2.39	
					25(0H)D	Quartile 4 (median 37.9ng/mL)	NR	47/118	adjusted/OR	1.38	0.73, 2.64	0.350
					1,25(OH)2D	Quartile 1 (median 25.5pg/mL)	NR	49/117	adjusted/OR	1	reference	
					1,25(OH)2D	Quartile 2 (median 31.2pg/mL)	NR	40/111	adjusted/OR	0.83	0.46, 1.49	
					1,25(OH)2D	Quartile 3 (median 34.7pg/mL)	NR	47/118	adjusted/OR	0.96	0.54, 1.68	
					1,25(OH)2D	Quartile 4 (median 41.1pg/mL)	NR	33/104	adjusted/OR	0.64	0.34, 1.19	0.220

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
				Primary-Rectal Cancer	25(0H)D	Quartile 1 (median 15.7ng/mL)	NR	20/44	adjusted/OR	1	reference	
					25(0H)D	Quartile 2 (median 22.3ng/mL)	NR	15/41	adjusted/OR	0.53	0.18, 1.60	
					25(0H)D	Quartile 3 (median 26.7ng/mL)	NR	9/37	adjusted/OR	0.42	0.13, 1.40	
					25(0H)D	Quartile 4 (median 37.9ng/mL)	NR	13/37	adjusted/OR	0.45	0.14, 1.46	0.050
					1,25(OH)2D	Quartile 1 (median 25.5pg/mL)	NR	20/44	adjusted/OR	1	reference	
					1,25(OH)2D	Quartile 2 (median 31.2pg/mL)	NR	13/37	adjusted/OR	0.57	0.20, 1.60	
					1,25(OH)2D	Quartile 3 (median 34.7pg/mL)	NR	10/36	adjusted/OR	0.43	0.13, 1.39	
					1,25(OH)2D	Quartile 4 (median 41.1pg/mL)	NR	12/36	adjusted/OR	0.75	0.27, 2.09	0.720

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Lee et al., 2011	Y	N	Y	Y						N

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	Y	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Lin et al., 2012	Prospective Cohort	19–50 years; 51–70 years; Healthy; 40–69 years	death before start of intervention		Government	China; Linxian	1101/1101/45	56.5 (7.9)/NR	Asian=100	Other; hypertension 27%	254 had serum vitamin D<19.6 nmol/L 278 had serum D of 19.6–31.8 nmol/L 262 had serum D of 31.9–48.3 nmol/L 307 had serum D of =48.4 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Lin et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI; Medical Conditions- Hypertension; Smoking, Other Lifestyle Factors- Tobacco Smoking, Alcohol	Primary-All-Cause Mortality	25(OH)D	continuous 25(OH)D	24 yrs	793/1101	adjusted/HR	1.01	0.97, 1.05	0.735
					25(OH)D	continuous 25(OH)D-men	24 yrs	479/608	adjusted/HR	0.99	0.94, 1.04	0.7
					25(OH)D	continuous 25(OH)D-women	24 yrs	314/493	adjusted/HR	1.03	0.97, 1.10	0.348
				Primary-Cancer Deaths	25(OH)D	continuous 25(OH)D	24 yrs	217/1101	adjusted/HR	0.97	0.89, 1.05	0.406
					25(OH)D	continuous 25(OH)D-men	24 yrs	141/608	adjusted/HR	1	0.91, 1.10	0.967
					25(OH)D	continuous 25(OH)D-women	24 yrs	76/493	adjusted/HR	0.88	0.75, 1.03	0.115
				Primary-Cerebrovascular Death	25(OH)D	continuous 25(OH)D	24 yrs	279/1101	adjusted/HR	1.05	0.98, 1.12	0.141
					25(OH)D	continuous 25(OH)D-men	24 yrs	157/608	adjusted/HR	1.04	0.96, 1.13	0.337
					25(OH)D	continuous 25(OH)D-women	24 yrs	122/493	adjusted/HR	1.06	0.96, 1.17	0.277
				Primary-Cardiovascular Death	25(OH)D	continuous 25(OH)D	24 yrs	200/1101	adjusted/HR	0.98	0.91, 1.06	0.678
					25(OH)D	continuous 25(OH)D-men	24 yrs	119/608	adjusted/HR	0.94	0.85, 1.04	0.223
					25(OH)D	continuous 25(OH)D-women	24 yrs	81/493	adjusted/HR	1.06	0.93, 1.20	0.399

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Lin et al., 2012	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	N	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Lips et al., 2010	RCT/CCT	ambulatory; mentally competent; If patients had serum 25(OH)D concentrations = 6 but = 9ng/mL; men and women	Current cancer; treatment with > or equal to .800 IU vitamin D/d or with active metabolites of vitamin D within 6 mo of screening; or treatment with any drug that might affect vitamin D metabolism or interfere with postural stability		Manufacturer	USA; 9 centers; Multiple Countries; Europe- 3 centers	213/213/NR	77.6 (6.6)/NR			serum vitamin D- placebo- 14.1+/-5.5 ng/ml, D3- 13.7+/-4.4 ng/ml serum calcium-placebo- 9.4+/- 0.4mg/dl, D3- 9.4+/- 0.4mg/dl

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Lips et al., 2010	RCT/CCT	NR	NR	Secondary-Short Physical Performance Battery (SPPB) Summary Score	Vit D3 8,400 IU/weekly		109	9.00 (SD=2.3)	change= 0.355 (0.108, 0.601)	-0.25 (-0.60, -0.10)	0.17
					Placebo		104	9.07 (SD=2.0)	change= 0.601 (0.351, 0.852)	reference (NR)	.
				Secondary-Short Physical Performance Battery (SPPB) Gait Speed	Vit D3 8,400 IU/weekly		109	93.70 (SD=31.5)	change= 3.10 (-0.252, 6.458)	-0.84 (-5.63, 3.95)	0.73
					Placebo		104	88.70 (SD=25.9)	change= 3.94 (0.567, 7.38)	reference (NR)	.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Lips et al., 2010	RCT/CCT	Y	ND	Y	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Looker et al., 2013	Prospective Cohort	51–70 years; >/=65 years	prior fracture; ineligible for linkage to the Medicare denominator file; enrolled in a HMO	NHANES III	Government	USA; multiple	4749/4749/74.3	75.2 (NR)/NR	Non-Hispanic White=925; Non-Hispanic Black=37; Race_other1=17; Race_other2=21	Not Reported	osteoporotic fracture- yes: 57.5 nmol/L, no: 60.1 nmol/L hip fracture- yes: 57.6 nmol/L, 60.0 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Looker et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race	Primary-Major Osteoporotic Fracture	25(OH)D	per 1 SD unit decline in serum 25OHD	7 yrs	400/4749	adjusted/RR	1.27	1.12, 1.44	
					25(OH)D	per 1 SD unit decline in serum 25OHD-65–79	7 yrs	212/NR	adjusted/RR	1.14	0.97, 1.34	
					25(OH)D	per 1 SD unit decline in serum 25OHD->=80	7 yrs	188/NR	adjusted/RR	1.4	1.13, 1.74	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Looker et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	reconciled

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Macdonald et al., 2013	RCT/CCT	51–70 years; Postmenopausal women; Healthy; 60–70 years of age; non-smoking	Type 2 DM; asthma; malabsorption; abnormal biochemical profile; blood pressure>160mm Hg systolic or >99 mm Hg diastolic; use of corticosteroids, anti-inflammatories, hypotensive, hypolipemic; unstable thyroid function; planned trips that would result in increased UV light exposure	Vitamin D and CardiOvascular Risk [VICtORy]	university	UK; Scotland	264/259/100	64.6 (2.3)/NR		Post menopausal	35.8±16.4 nmol/L

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Macdonald et al., 2013	RCT/CCT	Not relevant	Other Nutrients Or Dietary Factors- Calcium Intake; Smoking, Other Lifestyle Factors- Physical Activity	Secondary-Total Hip BMD	D3 400 IU		83	0.917 (sd=0.102)	final=0.912 (sd=0.103)	-0.002 (-0.036, 0.032)	0.91
					D3 1000 IU		88	0.923 (sd=0.132)	final=0.923 (sd=0.135)	+0.009 (-0.029, 0.047)	0.64
					placebo		88	0.92 (sd=0.118)	final=0.914 (sd=0.118)		.
				Secondary-Total Lumbar Spine BMD	D3 400 IU		83	1.075 (sd=0.141)	final=1.076 (sd=0.135)	+0.006 (-0.038, 0.050)	0.79
					D3 1000 IU		88	1.068 (sd=0.161)	final=1.071 (sd=0.164)	+0.001 (-0.046, 0.048)	0.97
					placebo		88	1.081 (sd=0.153)	final=1.070 (sd=0.153)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Macdonald et al., 2013	RCT/CCT	Y	Y	Y	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Magnus et al., 2013	Nested Case Control	Pregnant or lactating women; approximately 18 weeks gestation	Not specified	Norwegian Mother and Child Cohort Study	Private Foundation	Norway	1,248/1672/100	NR (NR)/NR			NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Magnus et al., 2013	Nested Case Control	unclear	Other Nutrients Or Dietary Factors- Maternal Multivitamin Use; Demographics (Age, Sex, Race/Ethnicity)- Maternal Age At Pregnancy, Education; Anthropometrics- Prepregnancy BMI; Medical Conditions- Maternal History Of Asthma; Sun Exposure- Season; Smoking, Other Lifestyle Factors- Smoking, Physical Activity	Primary-Asthma	25(OH)D	20 nmol/L increase in 25(OH)D	36 mos	489/1672	adjusted/OR	0.91	0.81, 1.02	
					25(OH)D	<51	36 mos	114/316	adjusted/OR	1	Reference	
					25(OH)D	51–75	36 mos	187/584	adjusted/OR	0.84	0.61, 1.17	
					25(OH)D	>75	36 mos	188/771	adjusted/OR	0.67	0.48, 0.95	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Magnus et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Mai et al., 2012	Nested Case Control	19–50 years; 51–70 years; 19 years or older; of Nord-Trondelag; 65 years or less	Not specified	HUNT study	Manufacturer	Nord-Trondelag, Norway	2613/2542/57	39.7 (8.5)/NR		Not Reported	women cases- 56.7 (23.7) nmol/L, controls- 59.5 (23.1) nmol/L men cases- 54.8 (20.8) nmol/L, controls- 58.9 (23.5) nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Mai et al., 2012	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Education; Anthropometrics- BMI; Sun Exposure- Season Of Blood Collection; Smoking, Other Lifestyle Factors- Daily Smoking, Physical Activity; Other - Allergic Rhinitis, Copd, Social Benefit, Economic Difficulties	Primary-Asthma	25(OH)D	>=75.0-female	11 yrs	81/328	adjusted/OR	1	Reference	
					25(OH)D	50.0–74.9-female	11 yrs	125/555	adjusted/OR	0.8	0.57, 1.13	
					25(OH)D	<50.0-female	11 yrs	170/566	adjusted/OR	0.94	0.67, 1.32	
					25(OH)D	each 25-nmol/L reduction-female	11 yrs	376/1449	adjusted/OR	0.97	0.85, 1.12	
					25(OH)D	>=75.0-male	11 yrs	33/247	adjusted/OR	1	Reference	
					25(OH)D	50.0–74.9-male	11 yrs	77/384	adjusted/OR	1.5	0.95, 2.38	
					25(OH)D	<50.0-male	11 yrs	98/462	adjusted/OR	1.47	0.93, 2.32	
					25(OH)D	each 25-nmol/L reduction-male	11 yrs	208/1093	adjusted/OR	1.14	0.94, 1.37	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Mai et al., 2012	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
McCullough et al., 2009	Nested Case Control	Not specified	pre or perimenopausal at baseline; no appropriate match; one or less vials of serum; extreme 25(OH)D level	Cancer Prevention Study-II (CPS-II)	Unclear	USA; 21 states	1032/1032/100	69.6 (5.8)/NR	Non-Hispanic White=971; Race_other1= 29		Plasma 25(OH)D cases- 56.5 (22.0) nmol/L controls- 56.2 (22.2) nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
McCullough et al., 2009	Nested Case Control	race, ethnicity, date of blood draw	Demographics (Age, Sex, Race/Ethnicity)- Birth Year, Race; Anthropometrics- Body Mass Index At Blood Collection, Weight Change From Age 18 Years To Blood Collection; Sun Exposure- Season; Other - Parity And Age At First Birth	Primary-Breast Cancer	25(0H)D	<36.7nmol/L	1month–6.9years	89/193	adjusted/OR	1	reference	
					25(0H)D	36.7<49.8nmol/L	1month–6.9years	115/217	adjusted/OR	1.29	0.86, 1.94	
					25(0H)D	49.8<60.8nmol/L	1month–6.9years	99/204	adjusted/OR	1.14	0.75, 1.72	
					25(0H)D	60.8<73.2nmol/L	1month–6.9years	118/220	adjusted/OR	1.44	0.96, 2.18	
					25(0H)D	>73.2nmol/L	1month–6.9years	95/198	adjusted/OR	1.09	0.70, 1,68	0.600

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
McCullough et al., 2009	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	Reconciled In the 2009 report: Population b) Y=random or consecutive, N=other sampling like convenience; Outcome c) NA for all observational studies. If we followed this, then this article would have grade A.

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Mena et al., 2013	Prospective Cohort	50–74 years of age between 2000 and 2002	Prior cancer; Current cancer; diagnosis of any type of cancer prior to baseline	Esther	Government	Germany (specify city, if given); Saarland	9,580/9007/46	NR (NR)/50–74			reported by season for each quartile

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Mena et al., 2013	Prospective Cohort	Not relevant	Other Nutrients Or Dietary Factors-; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Education; Anthropometrics- Obesity; Smoking, Other Lifestyle Factors- Smoking, Physical Activity; Other - Family History Of Cancer	Primary-Total Cancer	25(OH)D	Q1	8 yrs	235/2253	adjusted/HR	1.1	0.93, 1.30	
					25(OH)D	Q2+Q3	8 yrs	396/4500	adjusted/HR	1	Reference	
					25(OH)D	Q4	8 yrs	242/2254	adjusted/HR	1.12	0.95, 1.32	
				Primary-Prostate Cancer	25(OH)D	Q1	8 yrs	38/882	adjusted/HR	1.16	0.78, 1.74	
					25(OH)D	Q2+Q3	8 yrs	66/1737	adjusted/HR	1	Reference	
					25(OH)D	Q4	8 yrs	67/1505	adjusted/HR	1.21	0.86, 1.70	
				Primary-Breast Cancer	25(OH)D	Q1	8 yrs	38/1464	adjusted/HR	1.08	0.72, 1.60	
					25(OH)D	Q2+Q3	8 yrs	71/2951	adjusted/HR	1	Reference	
					25(OH)D	Q4	8 yrs	28/846	adjusted/HR	1.39	0.89, 2.18	
				Primary-Colorectal Cancer	25(OH)D	Q1	8 yrs	37/2373	adjusted/HR	1.02	0.68, 1.53	
					25(OH)D	Q2+Q3	8 yrs	69/4741	adjusted/HR	1	Reference	
					25(OH)D	Q4	8 yrs	30/2368	adjusted/HR	0.77	0.50, 1.20	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Mena et al., 2013	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Menant et al., 2012	Prospective Cohort	70–90 years; independent in ADLs = activities of daily living; able to walk 400m without assistance; community dwelling	multiple sclerosis; medical or psychological conditions that may prevent them from completing assessments; dementia or developmental disability; psychotic symptoms; Parkinson's disease; motor neuron disease; CNS inflammation	Memory and Ageing Study	Government	Australia; Sydney	463/926/54	78 (4.6)/70–90			serum vitamin D- 62.2±24.6 nmol/L;

Main Analyses (Dichotomous Outcomes)												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event / N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Menant et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Education; Anthropometrics- BMI	Primary-Falls In Men	25(OH)D	>= 50nmol/l	1 y	94/215	Crude/IRR	1.93	1.19, 3.15	0.008
					25(OH)D	> 50nmol/l	1y		Crude/IRR	1	Reference	
				Primary-Falls In Women	25(OH)D	>= 50nmol/l	1 y	115/248	Crude/IRR	0.83	0.56, 1.23	0.362
					25(OH)D	> 50nmol/l	1 y		Crude/IRR	1	Reference	

Main Analyses (Continuous Outcomes)											
Author,Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Menant et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Education; Anthropometrics- BMI	Secondary-Grip Strength	25(OH)D > 50 nmol/l		309	NR (NR)	final= 28.7 (SD=11.7)	+4.7 (3.3, 6.1)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 24.0 (SD=10.3)		.
				Secondary-Quadriceps Strength	25(OH)D > 50 nmol/l		309	NR (NR)	final= 28.9 (SD=11.9)	+6 (5, 7)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 22.9 (SD=10.4)		.
				Secondary-Finger Press Reaction Time	25(OH)D > 50 nmol/l		309	NR (NR)	final= 235.4 (SD=45.2)	-11.7 (NR)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 247.1 (SD=50.0)		.
				Secondary-Sway, Eyes Open-Floor	25(OH)D > 50 nmol/l		309	NR (NR)	final= 76.5 (SD=40.1)	-5.4 (-11.0, 0.2)	0.06
					25(OH)D = 50nmol/l		154	NR (NR)	final= 81.9 (SD=46.0)		.
				Secondary-Sway, Eyes Open-Foam	25(OH)D > 50 nmol/l		309	NR (NR)	final= 182.2 (SD=97.5)	-5.6 (-17.7, 6.5)	0.37
					25(OH)D = 50nmol/l		154	NR (NR)	final= 187.8 (SD=89.9)		.
				Secondary-Physiological Profile Assessment (PPA) Fall Risk Score	25(OH)D > 50 nmol/l		309	NR (NR)	final= 0.8 (SD=0.9)	-0.2 (-0.3, -0.1)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 1.0 (SD=0.9)		.
				Secondary-Maximal Balance Range	25(OH)D > 50 nmol/l		309	NR (NR)	final= 155.7 (SD=56.8)	+21.1 (14.2, 28.0)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 134.6 (SD=49.7)		.
				Secondary-Coordinated Stability Score	25(OH)D > 50 nmol/l		309	NR (NR)	final= 13.6 (SD=12.4)	-5.0 (-7, -3)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 18.6 (SD=13.3)		.
				Secondary-Choice Stepping Reaction Time	25(OH)D > 50 nmol/l		309	NR (NR)	final= 987.4 (SD=215.1)	-73.4 (-101.7, -45.1)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 1060.8 (SD=223.0)		.

Main Analyses (Continuous Outcomes)											
Author,Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
				Secondary-6 M Walk Speed	25(OH)D > 50 nmol/l		309	NR (NR)	final= 0.73 (SD=0.16)	+0.06 (0.04, 0.08)	.
					25(OH)D = 50nmol/l		154	NR (NR)	final= 0.67 (SD=0.17)		.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Menant et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Messenger et al., 2012	Prospective Cohort	51–70 years; 65 and older; men	inability to walk without assistance from another person; bilateral hip replacements; inability to provide self-reported data	Osteoporotic Fractures in Men Sleep Study MrOS	Government	USA; multiple	813/813/0	76.1 (5.6)/NR	Non-Hispanic White=91		quartiles

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Messenger et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Race, Sex; Anthropometrics- BMI; Medical Conditions- History Of Hypertension, Diabetes, And CV Event; Smoking, Other Lifestyle Factors- Smoking, Alcohol Use; Other - Diastolic BP, PASE Score, Statin Use, HDL, LDL, Triglycerides, Glucose, Insulin, Site And Season	Primary- Cardiovascular Disease(CHD & CVA)	25(OH)D	4.8–20.1 ng/ml	4.4 yrs (median)	39/204	Adjusted/HR	1.18	0.69, 2.03	0.85
					25(OH)D	20.2–25.2 ng/ml	4.4 yrs (median)	33/203	Adjusted/HR	1.11	0.65, 1.91	
					25(OH)D	25.3–30.0 ng/ml	4.4 yrs (median)	35/202	Adjusted/HR	0.97	0.57, 1.64	
					25(OH)D	30.1–55.4 ng/ml	4.4 yrs (median)	33/204	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Messenger et al., 2012	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Meyer et al., 2013	Nested Case Control	cases: new cases of prostate cancer; cases: donated serum>=1yr before diagnosis; Not specified	Prior cancer; controls: alive and free from cancer; missing data		Manufacturer	Norway- 17 of 19 counties	4212/4212/0	48.2 (9.2)/NR			serum vitamin D: cases- 64.4+/-22.2 nmol/L, controls- 62.4+/-22.3 nmol/L

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Meyer et al., 2013	Nested Case Control	age at serum sampling, date of serum sampling, county of residence	Demographics (Age, Sex, Race/Ethnicity)- Education; Sun Exposure- Month	Primary-Prostate Cancer	25(0H)D	<30nmol/L	NR	72/164	adjusted/RR	0.82	0.58, 1.15	
					25(0H)D	30–49nmol/L	NR	528/1081	adjusted/RR	1.02	0.87, 1.21	
					25(0H)D	50–69nmol/L	NR	718/1489	adjusted/RR	1	reference	
					25(0H)D	70–89nmol/L	NR	537/1003	adjusted/RR	1.24	1.05, 1.47	
					25(0H)D	>=90nmol/L	NR	251/475	adjusted/RR	1.17	0.93, 1.48	
					25(0H)D	30-nmol/L increase	NR	NR/4212	adjusted/RR	1.13	1.02, 1.25	
					25(0H)D	<30nmol/L-Winter and Spring	NR	49/112	adjusted/RR	0.8	0.52, 1.23	
					25(0H)D	30–49nmol/L-Winter and Spring	NR	304/590	adjusted/RR	1.09	0.86, 1.40	
					25(0H)D	50–69nmol/L-Winter and Spring	NR	288/585	adjusted/RR	1	reference	
					25(0H)D	70–89nmol/L-Winter and Spring	NR	145/273	adjusted/RR	1.14	0.85, 1.53	
					25(0H)D	>=90nmol/L-Winter and Spring	NR	38/88	adjusted/RR	0.74	0.46, 1.18	
					25(0H)D	30-nmol/L increase-Winter and Spring	NR	NR/1648	adjusted/RR	0.97	0.83, 1.14	
					25(0H)D	<30nmol/L-Summer and Autumn	NR	13/27	adjusted/RR	0.97	0.45, 2.10	
					25(0H)D	30–49nmol/L-Summer and Autumn	NR	132/304	adjusted/RR	0.87	0.66, 1.16	
					25(0H)D	50–69nmol/L-Summer and Autumn	NR	296/625	adjusted/RR	1	reference	
					25(0H)D	70–89nmol/L-Summer and Autumn	NR	297/625	adjusted/RR	1.34	1.05, 1.71	
					25(0H)D	>=90nmol/L-Summer and Autumn	NR	180/324	adjusted/RR	1.46	1.07, 2.00	
					25(0H)D	30-nmol/L increase-Summer and Autumn	NR	NR/1905	adjusted/RR	1.25	1.08, 1.45	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Meyer et al., 2013	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Michael et al., 2011	Prospective Cohort	51–70 years; 65–79 years	Not specified	WHI CT	Government	USA ;multiple	534/534/100	70.3 (3.7)/50–79	Non-Hispanic White=92; Hispanic=8; Race_other1=		serum vitamin D- 48.2+/- 21.4 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Michael et al., 2011	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Race/Ethnicity; Anthropometrics- BMI; Medical Conditions- Chronic Conditions; Sun Exposure- Clinic Latitude, Season, Time Walked Outside; Other - DM Trial Arm	Primary-Physical Performance Summary Score	25(OH)D	>= 75 nmol/l	6 y	NR/64	Adjusted/RR	3.66	1.88, 5.45	<0.001
					25(OH)D	50–74nmol/l	6 y	NR/148	Adjusted/RR	2.32	0.89, 3.75	
					25(OH)D	25–49 nmol/l	6 y	NR/255	Adjusted/RR	1.64	0.28, 3.01	
					25(OH)D	>= 25 nmol/l	6 y	NR/67	Adjusted/RR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Michael et al., 2011	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	eligibility criteria not clear from this article but exclusion criteria were probably named in the original studies exposure a unclear

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Michaelsson et al., 2010	Prospective Cohort	51–70 years; birth 1920–1924; Age approximately 71; male; Uppsala resident	Not specified	Uppsala Longitudinal Study of Adult Men	Swedish Research Council	Uppsala, Sweden	1,194/1194/0	71.0 (0.6)/NR		Other; more than 1/3 being treated for hypertension	For 10th–90th percentile: Mean Dietary Intake: 5.8ug/d(2.2) Mean total intake: 6.0ug/d (2.4) Plasma 25(OH)D: 46–93 nmol/L (18–37 ng/ml)

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Michaelsson et al., 2010	Prospective Cohort	NA	Other Nutrients Or Dietary Factors- Calcium Intake; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- Weight, Height; Medical Conditions- Hypertension, Type 2 Diabetes; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking Status; Other - Socioeconomic Status, Plasma PTH, Serum Calcium, Cystatin C, Serum Phosphate, Plasma Cholesterol, Self-Perceived Health	Primary-Overall Mortality	25(OH)D	< 10th percentile (<46 nmol/L)	12.7 yrs	76/119	adjusted/HR	1.43	1.11, 1.84	
					25(OH)D	10th–90th percentile (46–93 nmol/L)	12.7 yrs	444/956	adjusted/HR	1	Reference	
					25(OH)D	>90th percentile (>93 nmol/L)	12.7 yrs	64/119	adjusted/HR	1.27	0.97, 1.66	
				Primary-Cardiovascular Mortality	25(OH)D	< 10th percentile (<46 nmol/L)	12.7 yrs	24/119	adjusted/HR	1.53	0.97, 2.41	
					25(OH)D	10th–90th percentile (46–93 nmol/L)	12.7 yrs	135/956	adjusted/HR	1	Reference	
					25(OH)D	>90th percentile (>93 nmol/L)	12.7 yrs	18/119	adjusted/HR	1.16	0.69, 1.93	
				Primary-Cancer Mortality	25(OH)D	< 10th percentile (<46 nmol/L)	12.7 yrs	27/119	adjusted/HR	1.99	1.29, 3.08	
					25(OH)D	10th–90th percentile (46–93 nmol/L)	12.7 yrs	118/956	adjusted/HR	1	Reference	
					25(OH)D	>90th percentile (>93 nmol/L)	12.7 yrs	19/119	adjusted/HR	1.56	0.95, 2.56	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Michaelsson et al., 2010	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	didn't specify exclusion criteria

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Molgaard et al., 2010	RCT/CCT	9–18 years; girls; 11–12 years of age; Danish birth and citizenship	not specified; calcium or other vitamins or minerals; chronic diseases; intake of drugs that could influence bone metabolism		Government	Copenhagen and Frederiksberg Denmark	225/221/100	11.4 (0.2)/NR	Non-Hispanic White=100		Vitamin D intake: placebo-2.6±1.4ug/d Serum vitamin D level: placebo-43.4±17.1 nmol/L Calcium intake: placebo-955±588 mg/d

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Molgaard et al., 2010	RCT/CCT	age	Anthropometrics- Size - Bone And Body Size (The Outcome Is Adjusted Bone Mineral Content), Bone Area, Height, Weight; Other - Baseline Vitamin D, Tanner Stage, Vitamin D Receptor Genotype, Estrogen Receptor Genotype	Secondary-L1-L4 BMC	D3 10 µg Vit D3/day		74	28.9 (sd=6.4)	final=36.3 (sd=8.6)	-1.2 (-4.3, 1.9)	.
					D3 5 µg Vit D3/day		73	29.4 (sd=7.8)	final=37.6 (sd=10.3)	+0.1 (-3.2, 3.4)	.
					D3 placebo		74	29.2 (sd=7.7)	final=37.5 (sd=10.2)		.
				Secondary-L1-L4 BMD	D3 10 µg Vit D3/day		74	0.695 (sd=0.089)	final=0.780 (sd=0.113)	-0.01 (-0.05, 0.03)	.
					D3 5 µg Vit D3/day		73	0.698 (sd=0.092)	final=0.786 (sd=0.115)	-0.0 (-0.04, 0.04)	.
					D3 placebo		74	0.697 (sd=0.102)	final=0.788 (sd=0.121)		.
				Secondary-Whole Body BMD	D3 10 µg Vit D3/day		74	0.872 (sd=0.070)	final=0.917 (sd=0.080)	+0.01 (-0.02, 0.03)	.
					D3 5 µg Vit D3/day		73	0.866 (sd=0.066)	final=0.915 (sd=0.075)	+0.01 (-0.02, 0.03)	.
					D3 placebo		74	0.863 (sd=0.064)	final=0.909 (sd=0.075)		.
				Secondary-Whole Body BMC	D3 10 µg Vit D3/day		74	1308 (sd=303)	final=1561 (sd=366)	+38 (-74, 150)	.
					D3 5 µg Vit D3/day		73	1311 (sd=277)	final=1559 (sd=324)	+36 (-70, 142)	.
					D3 placebo		74	1277 (sd=273)	final=1523 (sd=324)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Molgaard et al., 2010	RCT/CCT	Y	ND	ND	Y	ND	ND	Y	Y	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Moschonis et al., 2010	RCT/CCT	51–70 years; Postmenopausal women; women; 55–65 years of age	Osteoporosis; Prior cancer; Current cancer; Current cardiovascular disease; Type 2 DM; thiazide diuretics, glucocorticoids,; calcium, vitamin D, magnesium, phosphorus; t-score<-2.5; any other degenerative chronic degenerative disease, e.g., nephrolithiasis, hyper- or hypothyroidism,, impaired liver or renal function; smoking; less than 1 year postmenopausal; abnormal values on hematologic and biochemical examinations; taking medications and/or dietary supplements that affect bone metabolism	Postmenopausal Health Study	Manufacturer	Greece	66/66/100	60.7 (5.0)/NR		Post menopausal	Vitamin D intake: 0.61±0.61 ug/d Serum vitamin D level:26.2±8.5 nmol/L Calcium intake: 682.9±226.1 mg/d

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Moschonis et al., 2010	RCT/CCT	Not described	NR	Secondary-Pelvis BMD	D3 (1200 mg calcium+7.5 µg D3)/day for the first 12 months + (1200 mg calcium+22.5 µg D3)/day for the next 18 months		35	1.096 (sd=0.078)	final=1.089 (sd=0.087)	+0.02 (-0.02, 0.06)	.
					D3 control (neither counselling nor dietary products)		31	1.067 (sd=0.102)	final=1.067 (sd=0.084)		.
				Secondary-Total Body BMD	D3 (1200 mg calcium+7.5 µg D3)/day for the first 12 months + (1200 mg calcium+22.5 µg D3)/day for the next 18 months		35	1.134 (sd=0.072)	final=1.135 (sd=0.067)	+0.03 (-0.01, 0.06)	.
					D3 control (neither counselling nor dietary products)		31	1.124 (sd=0.083)	final=1.106 (sd=0.078)		.
				Secondary-Total Spine BMD	D3 (1200 mg calcium+7.5 µg D3)/day for the first 12 months + (1200 mg calcium+22.5 µg D3)/day for the next 18 months		35	1.119 (sd=0.124)	final=1.234 (sd=0.135)	+0.04 (-0.03, 0.11)	.
					D3 control (neither counselling nor dietary products)		31	1.139 (sd=0.152)	final=1.193 (sd=0.139)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Moschonis et al., 2010	RCT/CCT	Y	ND	Y	Y	ND	N	ND	ND	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Moschonis et al., 2011	RCT/CCT	51–70 years; Postmenopausal women; Healthy; 55–65 years of age; self-dependent	Prior cancer; Current cancer; Current cardiovascular disease; Type 2 DM; e.g., thiazide diuretics, glucocorticoids; taking dietary supplements related to bone metabolism (calcium, magnesium, phosphorus, vitamin D); BMD T-score<-2.5; any bone degenerative chronic disease (nephrolithiasis, liver or kidney disease, cancer, hyper- or hypothyroidism, hyperparathyroidism; postmenopausal less than 1 year; taking medications or dietary supplements that affect bone metabolism; bone degenerative chronic disease; <1 year past menopause; smoking, osteoporosis, abnormal values on hematologic and biochemical examinations	Postmenopausal Health Study	Manufacturer	Greece	173/65/100	62.4 (5.3)/NR		Post menopausal	Vitamin D intake: 0.89±0.66ug/d Calcium intake: 789.6±213.5mg/d

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Moschonis et al., 2011	RCT/CCT	NR	NR	Secondary-Heel BMD	D3 CaD (800 mg calcium+10 µg Vit D3)/day		26	0.476 (sd=0.091)	final=0.459 (sd=0.081)	-0.002 (-0.04, 0.04)	.
					D3 control		39	0.472 (sd=0.083)	final=0.461 (sd=0.083)		.
				Secondary-L2-L4 BMD	D3 CaD (800 mg calcium+10 µg Vit D3)/day		26	1.121 (sd=0.158)	final=1.113 (sd=0.160)	+0.01 (-0.07, 0.10)	.
					D3 control		39	1.134 (sd=0.176)	final=1.101 (sd=0.167)		.
				Secondary-Total Body BMD	D3 CaD (800 mg calcium+10 µg Vit D3)/day		26	1.112 (sd=0.077)	final=1.135 (sd=0.083)	+0.04 (0, 0.08)	.
					D3 control		39	1.095 (sd=0.079)	final=1.094 (sd=0.079)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Moschonis et al., 2011	RCT/CCT	ND	ND	Y	Y	ND	N	ND	N	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Munger et al., 2013	Nested Case Control	Healthy; US Navy, MC active duty	Not specified		Government	USA	923/558/4.9	20.6 (4.0)/NR	Non-Hispanic White=607; Hispanic=126; Non-Hispanic Black=21; Not reported=54	Other; presumed healthy	Nested case control, so baseline vitamin D tertiles reported for cases and controls

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Munger et al., 2013	Nested Case Control	age, sex, race/ethnicity, dates of serum collection, and branch of active duty service (Navy or Marine Corps)	Sun Exposure- Latitudes Of State Of Residence Prior To Enlistment	Primary-Type 1 Diabetes Mellitus	25(0H)D	<75nmol/L-Cases with >=2 samples	5.4 years	45/102	Adjusted/RR	1	reference	
					25(0H)D	75–<100nmol/L-Cases with >=2 samples	5.4 years	76/236	Adjusted/RR	0.6	0.38, 0.97	
					25(0H)D	>=100nmol/L-Cases with >=2 samples	5.4 years	65/220	Adjusted/RR	0.56	0.35, 0.90	0.03

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Munger et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	**Justification of Final Adjusted Model Selection?**	**Clear Definition of Outcome Including Time of Ascertainment?**	**Loss to Followup <20%?**	**Do the Authors Specify a Primary Outcome?**	**Prospective Collection of Data?**	**Analysis Was Planned When Cohort Was Formed?**	**Justification of Sample Size (Includes Sample Size Calculations)?**	**Overall Grade**	**Explanation for Grade (if Not A)**
Y	N	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Murdoch et al., 2012	RCT/CCT	9–18 years; 19–50 years; 51–70 years; 18 years and older; staff or students of Canterbury District Health Board or University of Otago; able to give written informed consent; anticipating residence in Christchurch for the study period	Consumption of vitamin D supplements other than as part of a daily multi with a daily intake =400IU; Current cancer; Pregnant; history of hypercalcemia or nephrolithiasis; use of immuno-suppressants or medications that interfere with vitamin D metabolism (e.g., thiazide diuretics, phenytoin, carbamazepine, primidone, phenobarbital, prednisone>10mg/d, methotrexate, azathioprine, cyclosporine); sarcoidosis; kidney disorders requiring dialysis or polycystic kidney disease; cirrhosis; baseline plasma calcium corrected for albumin>10.4mg/dL or <8.4mg/dL; Enrollment or planned enrollment in other research study that would conflict with the present study; planned pregnancy during the study period	VIDARIS	Government	New Zealand	322/322/75	48 (10)/NR	Non-Hispanic White=93; Asian=3; Not reported=2; Race_other1=4; Race_other2=1	Not Reported	Serum vitamin D level:28±9 ng/ml Plasma calcium: 9.2±0.4 mg/dL

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Murdoch et al., 2012	RCT/CCT	NR	NR	Primary-Number of URTIs per Person	Vit D3 & Placebo	100,000IU-NR	18 months	3.7/161	Adjusted/RR	0.97	0.85,1.11	0.65
					Vit D3 & Placebo	Placebo-NR	18 months	3.7/161	Adjusted/RR	1	reference	
				Primary-No Of Days If Missed Work Per Episode	Vit D3 & Placebo	100,000IU-NR	18 months	0.76/161	Adjusted/RR	1.03	0.81, 1.30	0.82
					Vit D3 & Placebo	Placebo-NR	18 months	0.76/161	Adjusted/RR	1	reference	
				Primary-Duration Of Symptoms	Vit D3 & Placebo	100,000IU-NR	18 months	12/161	Adjusted/RR	0.96	0.73, 1.25	0.76
					Vit D3 & Placebo	Placebo-NR	18 months	12/161	Adjusted/RR	1	reference	

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Murdoch et al., 2012	RCT/CCT	Y	ND	Y	Y	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Neuhouser et al., 2012	Nested Case Control	Same as for CRC cohort	Same as for CRC cohort	Women's Health Initiative Calcium and Vitamin D Clinical Trial	Government	USA; multiple cities	2,160/2160/100	62.4 (6.9)/NR	Non-Hispanic White=783; Hispanic=36; Non-Hispanic Black=151; Not reported=30	Post menopausal	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Neuhouser et al., 2012	Nested Case Control	NR	NR	Primary-Colorectal Cancer	25(0H)D	>=64.5nmol/L	NR	231/500	adjusted/OR	1	reference	
					25(0H)D	43.6<64.5nmol/L	NR	250/520	adjusted/OR	2.76	1.30, 5.89	
					25(0H)D	32.7<43.6nmol/L	NR	306/578	adjusted/OR	1.51	0.72, 3.14	
					25(0H)D	<32.7nmol/L	NR	293/562	adjusted/OR	4.45	1.96, 10.10	0.003

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Neuhouser et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	cancers confirmed by medical record review by health professionals

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Neuhouser et al., 2012	Nested Case Control	19–50 years; 51–70 years; Postmenopausal women; 50–79 years of age; If age=55, no menstrual period for at least 6 months; If age 50–54, no menstrual period for at least 12 months; life expectancy of at least 3 years	calcitriol or =600IU vitamin D per day; Hypertension; daily corticosteroids; any invasive cancer in prior 10 years, breast cancer at any time, suspicious mammography findings; MI in prior 6 months; stroke or TIA in prior 6 months; history of renal calculi or hypercalcemia; mental illness, dementia, alcohol or drug dependency; any medical condition with predicted survival < 3 years; chronic hepatitis, severe cirrhosis; severe underweight or anemia	WHI	Government	USA; multiple cities	620/620/100	65.1 (6.8)/NR	Non-Hispanic White=757; Hispanic=44; Non-Hispanic Black=171; Not reported=28	Post menopausal	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Neuhouser et al., 2012	Nested Case Control	age, latitude of the clinical center (or clinical center location if latitude was not available), race/ethnicity, and blood collection date	Other Nutrients Or Dietary Factors- Vitamin D, Calcium, Red Meat Intake; Demographics (Age, Sex, Race/Ethnicity)- Age, Race; Anthropometrics- BMI, Waist Circumference; Smoking, Other Lifestyle Factors- Smoking, Physical Activity, Alcohol Use; Other - Screening For CRC, Use Of Hormone Therapy	Primary-Breast Cancer	25(0H)D	>=64.9nmol/L	NR	53/130	adjusted/OR	1	reference	
					25(0H)D	50.9<64.9nmol/L	NR	84/162	adjusted/OR	0.99	0.75, 1.31	
					25(0H)D	36.7<50.9nmol/L	NR	68/147	adjusted/OR	1.11	0.83, 1.49	
					25(0H)D	<36.7nmol/L	NR	105/181	adjusted/OR	1.06	0.78, 1.43	0.600

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Neuhouser et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	cancers confirmed by medical record review by health professionals

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Ng et al., 2009	RCT/CCT	19–50 years; 51–70 years; ambulatory; 18–80 years; stable medical condition; no change in medications for 6 months prior to study entry	Current cancer; Pregnant; current liver or kidney disorders; BMI >35 kg/m2; current tobacco use; h/o hypercalcemia, nephrolithiasis, sarcoidosis; recent hospitalization; malignancy and malabsorption; medications that interfere with vitamin D metabolism such as phenytoin and carbamazepine; use of immunosuppressants		Government	USA; Long Island, NY	162/296/79.7	58.1 (13.4)/NR	Non-Hispanic White=885; Non-Hispanic Black=41; Asian=54; Race_other1= 20		The baseline 25-OHD levels ranged from 16 to 156 nmol/l with a mean level of 63.7+/-28.7 nmol/l in the study population. serum vitamin D: active- 64.3+/-5.4 nmol/L, placebo- 63.0+/-25.8 nmol/L calcium intake: active- 762.8+/-375.7 mg/d, placebo- 854.6+/-

Main Analyses (Dichotomous Outcomes)												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event / N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Ng et al., 2009	RCT/CCT	NR	NR	Primary-Upper Respiratory Tract	Vit D; IU/day	2000IU/day	12 weeks	28/78	Crude/OR	0.79	0.41, 1.54	0.61%
						Placebo	12 weeks	29/70	Crude/OR	1	reference	

Main Analyses (Continuous Outcomes)											
Author,Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Ng et al., 2009	RCT/CCT	NR	NR	Secondary-Duration Of Upper Respiratory Tract	Vit D 2000IU/day		78	NR (NR)	final=5.4 (SD=4.8)	+1.0 (-1.2, 1.4)	0.86
					Placebo		70	NR (NR)	final=5.3 (SD=3.1)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Ng et al., 2009	RCT/CCT	Y	ND	ND	Y	Y	N	Y	ND	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Nieves et al., 2012	RCT/CCT	19–50 years; Postmenopausal women; women; Black; age over 45; natural spontaneous menopause or surgical ovariectomy at least 1 year prior to recruitment	Other systemic bone disease (e.g., Paget's); Current cancer; Current cardiovascular disease; Type 2 DM; Autoimmune disease; in the preceding 6 months; cardiac and pulmonary conditions; gastrointestinal, hepatic, and renal diseases; active hyperthyroidism; treatment with insulin, oral hypoglycemic agents, or thyroid hormone; smoking; drug abuse; rheumatoid arthritis		Government	USA; New York	127/103/100	61.2 (7.6)/NR	Non-Hispanic Black=100	Vitamin d deficient/depleted; Post menopausal	Serum 25(OH)D: 11.6±5.7 ng/ml

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Nieves et al., 2012	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI	Secondary-Femoral Neck BMD	D3 1,000 IU Vit D3		55	NR (NR)	change=-0.2 (NR)	+0.6 (NC)	.
					D3 placebo		48	NR (NR)	change=-0.8 (NR)		.
				Secondary-Spine BMD	D3 1,000 IU Vit D3		55	1.154 (sd=0.16)	change=-0.5 (NR)	+0.1 (NC)	.
					D3 placebo		48	1.212 (sd=0.15)	change=-0.6 (NR)		.
				Secondary-Total Hip BMD	D3 1,000 IU Vit D3		55	1.043 (sd=0.14)	change=-0.5 (NR)	+0.2 (NC)	.
					D3 placebo		48	1.04 (sd=0.13)	change=-0.7 (NR)		.
				Secondary-Trochanter BMD	D3 1,000 IU Vit D3		55	NR (NR)	change=-0.3 (NR)	+0.15 (NC)	.
					D3 placebo		48	NR (NR)	change=-0.45 (NR)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Nieves et al., 2012	RCT/CCT	ND	ND	ND	Y	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Oeffelen et al., 2011	Prospective Cohort	3–8 years; newborns of mothers visiting prenatal clinics assessed at 4- and 8-years of age	Not specified	Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study	Government	The Netherlands	3963/862/48.1	NR/NR		Not Reported	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Oeffelen et al., 2011	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Gender; Smoking, Other Lifestyle Factors- Smoking In The House At 3 Months Of Age	Primary-Bronchial Hyperresponsiveness	25(OH)D	Tertile 1: range 23.1–60.2 nm	8 yrs	80/204	adjusted/OR	1	Reference	
					25(OH)D	Tertile 2: range 60.7–78.8 nm	8 yrs	88/209	adjusted/OR	1.16	0.62, 2.18	
					25(OH)D	Tertile 3: range 79.0–303.8 nm	8 yrs	87/194	adjusted/OR	1.19	0.63, 2.23	
				Primary-Atopy	25(OH)D	Tertile 1: range 23.1–60.2 nm	8 yrs	93/346	adjusted/OR	1	Reference	
					25(OH)D	Tertile 2: range 60.7–78.8 nm	8 yrs	101/237	adjusted/OR	2.19	1.17, 4.12	
					25(OH)D	Tertile 3: range 79.0–303.8 nm	8 yrs	93/279	adjusted/OR	1.23	0.64, 2.39	
				Primary-Asthma	25(OH)D	Tertile 1: range 23.1–60.2 nm	5–8 yrs	NR/NR	adjusted/OR	1	Reference	
					25(OH)D	Tertile 2: range 60.7–78.8 nm	5–8 yrs	NR/NR	adjusted/OR	0.97	0.57, 1.65	
					25(OH)D	Tertile 3: range 79.0–303.8 nm	5–8 yrs	NR/NR	adjusted/OR	0.68	0.39, 1.19	
				Primary-Severe Asthma	25(OH)D	Tertile 1: range 23.1–60.2 nm	5–8 yrs	NR/NR	adjusted/OR	1	Reference	
					25(OH)D	Tertile 2: range 60.7–78.8 nm	5–8 yrs	NR/NR	adjusted/OR	1.06	0.59, 1.90	
					25(OH)D	Tertile 3: range 79.0–303.8 nm	5–8 yrs	NR/NR	adjusted/OR	0.61	0.32, 1.15	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Oeffelen et al., 2011	Y	Y	N	Y				Y	Y	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	Y	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Park et al., 2010	Nested Case Control	19–50 years; 51–70 years; men; 45–75 years of age; living in Hawaii or California	Not specified	Multiethnic Cohort Study	Government	USA; CA and HI	985/985/0	68.7 (7.2)/NR	Non-Hispanic White=166; Hispanic=159; Non-Hispanic Black=415; Race_other1= 35; Race_other2= 226	Not Reported	Serum vitamin D level:33.1±15.5 ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Park et al., 2010	Nested Case Control	age at blood draw, fasting hours, season of blood draw	Other Nutrients Or Dietary Factors- Calcium Intake; Vitamin D Intake; Anthropometrics- BMI; Other - Physical Activity Level, Family History Of Prostate Cancer	Primary-Prostate Cancer	25(0H)D	Q1:<22.9ng/mL	NR	82/245	adjusted/OR	1	reference	
					25(0H)D	Q2: 22.9<31.0ng/mL	NR	84/250	adjusted/OR	1.05	0.70, 1.58	
					25(0H)D	Q3: 31.0<39.9ng/mL	NR	72/244	adjusted/OR	0.81	0.52, 1.28	0.470
					25(0H)D	Q4: >=39.9ng/mL	NR	91/246	adjusted/OR	1.17	0.72, 1.89	0.600
					25(0H)D	Deficient: <20ng/mL	NR	53/159	adjusted/OR	1.1	0.68, 1.78	
					25(0H)D	Insufficient: 20<30ng/mL	NR	98/302	adjusted/OR	1.04	0.73, 1.48	
					25(0H)D	30<50ng/mL	NR	137/424	adjusted/OR	1	reference	0.170
					25(0H)D	>=50ng/mL	NR	41/100	adjusted/OR	1.52	0.92, 2.51	0.320

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Park et al., 2010	N	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	No exclusion criteria listed or anything about how many people actually received the survey and how they were chosen...

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Perna et al., 2013	Prospective Cohort	19–50 years; 51–70 years; residence in the state of Saarland,; sufficient knowledge of the German; age 50–74 years	history of CVD; unknown history of CVD; missing baseline measurements of 25(OH)D	ESTHER	Government	Germany (specify city, if given);Saarland	7709/7709/59.3	NR/50–74		Other; 46.3% hypertension	14.5% of population had serum D of <30 nmol/L, 44.5%- 31–<50 nmol/L, 41.1% >/= 50 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Perna et al., 2013	Prospective Cohort	NA	Other Nutrients Or Dietary Factors- Regular Multivitamin Supplement Intake; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI; Medical Conditions- Hypertension, DM, CKD; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking, Physical Activity; Other - CRP, Family History Of CVD, Fish Consumption	Primary-Total Cvd	25(OH)D	< 30	6.5 yrs	171/1114	adjusted/HR	1.24	1.02, 1.50	
					25(OH)D	30–<50	6.5 yrs	448/3430	adjusted/HR	1.14	0.99, 1.32	
					25(OH)D	>=50	6.5 yrs	392/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	1011/7709	adjusted/HR	0.95	0.89, 1.01	
				Primary-Nonfatal Cvd	25(OH)D	< 30	6.5 yrs	136/1114	adjusted/HR	1.17	0.94, 1.45	
					25(OH)D	30–<50	6.5 yrs	383/3430	adjusted/HR	1.15	0.98, 1.35	
					25(OH)D	>=50	6.5 yrs	335/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	854/7709	adjusted/HR	0.98	0.91, 1.05	
				Primary-Fatal Cvd	25(OH)D	< 30	6.5 yrs	40/1114	adjusted/HR	1.55	1.01, 2.37	
					25(OH)D	30–<50	6.5 yrs	71/3430	adjusted/HR	1.05	0.73, 1.49	
					25(OH)D	>=50	6.5 yrs	65/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	176/7709	adjusted/HR	0.89	0.66, 0.94	
				Primary-Total Chd	25(OH)D	< 30	6.5 yrs	92/1114	adjusted/HR	1.32	1.02, 1.72	
					25(OH)D	30–<50	6.5 yrs	236/3430	adjusted/HR	1.19	0.98, 1.45	
					25(OH)D	>=50	6.5 yrs	208/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	536/7709	adjusted/HR	0.92	0.84, 1.01	
				Primary-Nonfatal Chd	25(OH)D	< 30	6.5 yrs	77/1114	adjusted/HR	1.28	0.97, 1.71	
					25(OH)D	30–<50	6.5 yrs	204/3430	adjusted/HR	1.18	0.95, 1.46	
					25(OH)D	>=50	6.5 yrs	179/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	460/7709	adjusted/HR	0.96	0.88, 1.06	
				Primary-Fatal Chd	25(OH)D	< 30	6.5 yrs	16/1114	adjusted/HR	1.53	0.80, 2.94	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	30–<50	6.5 yrs	32/3430	adjusted/HR	1.18	0.70, 1.99	
					25(OH)D	>=50	6.5 yrs	31/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	79/7709	adjusted/HR	0.7	0.54, 0.93	
				Primary-Total Stroke	25(OH)D	< 30	6.5 yrs	64/1114	adjusted/HR	1.31	0.95, 1.81	
					25(OH)D	30–<50	6.5 yrs	165/3430	adjusted/HR	1.2	0.94, 1.54	
					25(OH)D	>=50	6.5 yrs	124/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	353/7709	adjusted/HR	0.91	0.81, 1.02	
				Primary-Nonfatal Stroke	25(OH)D	< 30	6.5 yrs	55/1114	adjusted/HR	1.26	0.89, 1.77	
					25(OH)D	30–<50	6.5 yrs	146/3430	adjusted/HR	1.19	0.92, 1.55	
					25(OH)D	>=50	6.5 yrs	112/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	313/7709	adjusted/HR	0.91	0.81, 1.02	
				Primary-Fatal Stroke	25(OH)D	< 30	6.5 yrs	9/1114	adjusted/HR	1.86	0.74, 4.66	
					25(OH)D	30–<50	6.5 yrs	20/3430	adjusted/HR	1.44	0.68, 3.03	
					25(OH)D	>=50	6.5 yrs	12/3165	adjusted/HR	1	reference	
					25(OH)D	per 25	6.5 yrs	41/7709	adjusted/HR	0.86	0.61, 1.23	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Perna et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Pfeifer et al., 2009	RCT/CCT	51–70 years; healthy; 70 years of age and older; serum vitamin D<78nmol/L	vitamin D and vitamin D metabolites; Osteoporosis; Prior fragility fracture; Pregnant; Severe cardiovascular disease; chronic renal failure, history of drug, alcohol, tobacco, caffeine abuse; hypercalcemia; primary hyperparathyroidism; diabetes mellitus		Manufacturer	Germany (specify city, if given);Bad Pyrmont; Graz, Austria	242/470/74	77 (4)/NR			Serum vitamin D level:55±18 nmol/L Calcium intake: 608±38 mg/d

Main Analyses (Dichotomous Outcomes)												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event / N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Pfeifer et al., 2009	RCT/CCT	age height weight gender serum 25(OH)D nutritional calcium intake intact PTH levels	NR	Primary-Falls (>=1)	Vit D3; Ca	1000 mg & 800 IU daily	12 mo	NR/122	Crude/RR	0.73	0.54, 0.96	<0.01
					Ca	1000 mg daily	12 mo	NR/120	Crude/RR	1	Reference	

Main Analyses (Continuous Outcomes)											
Author,Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Pfeifer et al., 2009	RCT/CCT	age height weight gender serum 25(OH)D nutritional calcium intake intact PTH levels	NR	Secondary-Quadriceps Strength Left Leg	Ca & Vit D3 1000 mg & 800 IU daily		114	211.00 (SD=83)	final= 236 (SD=75)	+12 (-8.6, 32.6)	0.25
					Ca 1000 mg daily		114	217.00 (SD=90)	final= 224 (SD=83)		.
				Secondary-Body Sway Total Length	Ca & Vit D3 1000 mg & 800 IU daily		114	86.00 (SD=32)	final= 81 (SD=32)	-5 (-13, 3)	0.22
					Ca 1000 mg daily		114	90.00 (SD=42)	final= 86 (SD=30)		.
				Secondary-Timed Up And Go (Tug)	Ca & Vit D3 1000 mg & 800 IU daily		114	9.00 (SD=5.9)	final= 7.5 (SD=3.4)	-0.8 (-1.9, 0.3)	0.16
					Ca 1000 mg daily		114	8.50 (SD=3.9)	final= 8.3 (SD=5.1)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Pfeifer et al., 2009	RCT/CCT	ND	ND	Y	Y	Y	Y	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Pike et al., 2012	Prospective Cohort	women 20–34 years; children born to these women from 1998 to 2002	infants born at<35 weeks gestation		Private Foundation	UK	860/836/48.26 (children)	30.37 (3.81)/NR		Other; mother/child pairs: slightly more than 20% of mothers had history of asthma and nearly half had atopy	Maternal late serum vitamin D: median 59.00 nmol/L (IQR:40.52–84.89)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Pike et al., 2012	Prospective Cohort	NR	NR	Primary-Current Doctor-Diagnosed Asthma	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	87/836	adjusted/RR	0.98	0.92, 1.04	0.56
				Primary-Current Wheeze In Last 12 Months	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	117/833	adjusted/RR	0.99	0.94, 1.05	0.76
				Primary-Any Wheeze At Or Before 6 Years	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	504/823	adjusted/RR	1	0.98, 1.02	0.95
				Primary-Transient Wheeze	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	367/707	adjusted/RR	1	0.98, 1.02	0.89
				Primary-Persistent Late Wheeze	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	137/475	adjusted/RR	0.98	0.94, 1.03	0.49
				Primary-Persistent Late Wheeze With Atopy	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	46/251	adjusted/RR	0.91	0.84, 0.99	0.04
				Primary-Persistent Late Wheeze Without Atopy	25(OH)D	per 10 nmol/l rise in CB 25(OH)D3	6 yrs	48/253	adjusted/RR	1.01	0.94, 1.09	0.73

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Pike et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	Y	N	B	>20% lost to follow-up but had partial data. Not sure whether sufficient

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Pilz et al., 2009	Prospective Cohort	19–50 years; 51–70 years; 50–75 years of age	Not specified	Hoorn Study	Private Foundation	Hoorn, Netherlands	614/614/50	69.2 (3rd quartile) (6.5)/NR	Non-Hispanic White=100	Other; more than 20% Type 2 Diabetes or impaired glucose tolerance	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Pilz et al., 2009	Prospective Cohort	NA	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- Waist-To-Hip Ratio, Percent Body Fat; Medical Conditions- Hypertension; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking, Physical Activity; Other - HDL Cholesterol, Glomerular Filtration Rate	Primary-All-Cause Mortality	25(OH)D	1st quartile (mean 25(OH)D 30.6 nmol/L)	6.2 yrs	21/152	adjusted/HR	1.97	1.08, 3.58	0.027
					25(OH)D	2nd–4th quartiles (mean 25(OH)D 45.6–78.9)	6.2 yrs	30/462	adjusted/HR	1	Reference	
				Primary-Cardiovascular Mortality	25(OH)D	1st quartile (mean 25(OH)D 30.6 nmol/L)	6.2 yrs	12/152	adjusted/HR	5.38	2.02, 14.34	0.001
					25(OH)D	2nd–4th quartiles (mean 25(OH)D 45.6–78.9)	6.2 yrs	8/462	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Pilz et al., 2009	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	N	N	B	Alicia didn't actually record selections. Large loss to followup.

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Powe et al., 2010	Nested Case Control	Pregnant or lactating women; nulliparous; Delivering singleton live births after 20 weeks gestation	Hypertension; history of diabetes; thyroid, liver, chronic renal disease; pre-existing chronic hypertension	MGH Obstetric Maternal Study	Private Foundation	USA; Boston	170/NR/100	30.4 (6.0)/NR	Non-Hispanic White=664	Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Powe et al., 2010	Nested Case Control	gestational age at blood draw	Demographics (Age, Sex, Race/Ethnicity)- BMI, Race; Sun Exposure- Season Of Blood Draw; Other - Gestational Age At Blood Collection	Primary-Severe Preeclampsia	25(OH)D	Quartile 1 (ND)	NR	39 (overall)/ NR	adjusted/OR	1.5	0.57, 3.96	
					25(OH)D	Quartile 2 (ND)	NR		adjusted/OR	1.04	0.39, 2.76	
					25(OH)D	Quartile 3 (ND)	NR		adjusted/OR	0.67	0.23, 1.91	
					25(OH)D	Quartile 4 (ND)	NR		adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Powe et al., 2010	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Prentice et al., 2013	RCT/CCT	Postmenopausal women; age 50–79; intending to reside in area for =3 years	intention to continue taking = 600 IU per day; current use of calcitriol; current use of daily corticosteroids; Any invasive cancer in prior 10 years, breast cancer, no mammogram within 2 years prior to enrollment; self-reported urinary tract stones	WHI	Private Foundation	USA; multiple sites	36,282/30604/ 100	50–54: 14.2%; 55–59: 22.8%; 60–69: 45.5%; 70–79: 17.5%/50–79	Non-Hispanic White=831; Hispanic=42; Non-Hispanic Black=91; Asian=20; Race_other1= 04; Race_other2= 12	Post menopausal	NR

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Prentice et al., 2013	RCT/CCT	NR	Other Nutrients Or Dietary Factors- Usual Intake Of Vitamin D And Calcium; Demographics (Age, Sex, Race/Ethnicity)- Baseline Age, Non-White Ethnicity; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Current Or Past Cigarette Smoking	Primary-Total Fracture	D3; calcium carbonate	1000mg/day of Ca & 400IU/day of Vit D3	7.2 yrs	872/7718	adjusted/HR	0.97	0.88, 1.07	NR
						placebo	7.2 yrs	870/7584	adjusted/HR	1	reference	
				Primary-Hip Fracture	D3; calcium carbonate	1000mg/day of Ca & 400IU/day of Vit D3	7.2 yrs	68/7718	adjusted/HR	0.86	0.62, 1.20	NR
						placebo	7.2 yrs	80/7584	adjusted/HR	1	reference	
				Primary-Total Invasive Cancer	D3; calcium carbonate	1000mg/day of Ca & 400IU/day of Vit D3	7.2 yrs	553/7718	adjusted/HR	0.88	0.78, 0.98	NR
						placebo	7.2 yrs	617/7584	adjusted/HR	1	reference	
				Primary-Death	D3; calcium carbonate	1000mg/day of Ca & 400IU/day of Vit D3	7.2 yrs	331/7718	adjusted/HR	0.95	0.81, 1.11	NR
						placebo	7.2 yrs	338/7584	adjusted/HR	1	reference	
				Primary-MI	25(OH)D3; calcium carbonate	1000mg/day of Ca & 400IU/day of Vit D3	7 yrs	193/7718	Adjusted/HR	1.18	0.88, 1.59	0.17
						placebo	7 yrs	167/7584	Adjusted/HR	1	Reference	
				Primary-Coronary Heart Disease	25(OH)D3; calcium carbonate	1000mg/day of Ca & 400IU/day of Vit D3	7 yrs	229/7718	Adjusted/HR	1.08	0.82, 1.42	0.4
						placebo	7 yrs	211/7584	Adjusted/HR	1	Reference	
				Primary-Total Heart Disease	25(OH)D3; calcium carbonate	1000mg/day of Ca & 400IU/day of Vit D3	7 yrs	621/7718	Adjusted/HR	1	0.86, 1.18	0.56
						placebo	7 yrs	642/7584	Adjusted/HR	1	Reference	
				Primary-Stroke	25(OH)D3; calcium carbonate	1000mg/day of Ca & 400IU/day of Vit D3	7 yrs	184/7718	Adjusted/HR	1.18	0.86, 1.62	0.96
						placebo	7 yrs	162/7584	Adjusted/HR	1	Reference	
				Primary-Total Cardiovascular Disease	25(OH)D3; calcium carbonate	1000mg/day of Ca & 400IU/day of Vit D3	7 yrs	848/7718	Adjusted/HR	1.04	0.90, 1.19	0.77
						placebo	7 yrs	813/7584	Adjusted/HR	1	Reference	

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Prentice et al., 2013	RCT/CCT	Y	Y	N	N	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Prince et al., 2008	RCT/CCT	51–70 years; older women; history of falling in the prior 12 months; serum vitamin D<24.0ng/ml	current vitamin D consumption; Other systemic bone disease (e.g., Paget's); current consumption of bone or mineral active agents other than calcium; bone mineral density z-score at the hip of <-2.0; fracture in the past 6 months; marked neurological conditions; medical conditions that influence bone mineral metabolism		Manufacturer	Australia;Perth	302/302/100	77.4 (5.0)/70–90		Vitamin d deficient/depleted	Serum vitamin D: 17.7±5.1 ng/mL

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Prince et al., 2008	RCT/CCT	NR	NR	Primary-Falls (>=1)	Vit D2; Ca	1000mg of Ca & 1000 IU of Vit D2 daily	1 y	80/151	Adjusted/OR	0.61	0.37, 0.99	< 0.05
					placebo; Ca	1000mg of Ca & placebo daily	1 y	95/151	Adjusted/OR	1	Reference	
				Primary-1 Fall	Vit D2; Ca	1000mg of Ca & 1000 IU of Vit D2 daily	1 y	32/151	Crude/OR	0.5	0.28, 0.88	< 0.05
					placebo; Ca	1000mg of Ca & placebo daily	1 y	51/151	Crude/OR	1	Reference	
				Primary-Falls (=2)	Vit D2; Ca	1000mg of Ca & 1000 IU of Vit D2 daily	1 y	NR/151	Crude/OR	0.86	0.50, 1.49	> 0.05
					placebo; Ca	1000mg of Ca & placebo daily	1 y	NR/151	Crude/OR	1	Reference	
				Primary-First Fall In Winter/Spring	Vit D2; Ca	1000mg of Ca & 1000 IU of Vit D2 daily	1 y	38/151	Crude/OR	0.55	0.32, 0.96	< 0.05
					placebo; Ca	1000mg of Ca & placebo daily	1 y	54/151	Crude/OR	1	Reference	
				Primary-First Fall In Summer/Autumn	Vit D2; Ca	1000mg of Ca & 1000 IU of Vit D2 daily	1 y	42/151	Crude/OR	0.81	0.46, 1.42	> 0.05
					placebo; Ca	1000mg of Ca & placebo daily	1 y	41/151	Crude/OR	1	Reference	

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Prince et al., 2008	RCT/CCT	Y	ND	Y	Y	Y	N	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Racovan et al., 2012	RCT/CCT	19–50 years; 51–70 years; Postmenopausal women; 50–79 years at baseline; no evidence of a medical condition associated with a predicted survival of less than 3 years	calcitriol use; corticosteroid use; hypercalcemia, renal calculi	WHI	Government	USA; multiple	32,435/32521/ 100	62.34 (6.91)/NR	Non-Hispanic White=8415; Hispanic=382; Non-Hispanic Black=846; Asian=203; Race_other1= 120; Race_other2= 035	Post menopausal	categories: <200, 200–<400, 400–<600, >/=600 IU/day

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Racovan et al., 2012	RCT/CCT	Age, race/ethnicity, BMI, solar irradiance, total vitamin D intake, multivitamin use, education, HT, smoking history, alcohol consumption, or breastfeeding history.	NR	Primary-Rheumatoid Arthritis	Vit D; Calcium 1000ng	400IU-NR	5.1 years	45/16283	Adjusted/HR	1.15	0.75, 1.75	0.53
					Vit D; Calcium 1000ng	Placebo-NR	5.1 years	41/16238	Adjusted/HR	1	reference	

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Racovan et al., 2012	RCT/CCT	Y	Y	NA	N	ND	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Rejnmark et al., 2009	Nested Case Control	Referred for mammogram; No previous breast cancer	Not specified		Private Foundation	Denmark	562/NR/100	58/29–87			

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Rejnmark et al., 2009	Nested Case Control	age, menopausal status, season of blood draw, body weight, calcium intake, smoking habits, fresh fruit consumption, alcohol intake	NR	Primary-Breast Cancer	25(0H)D	<60nmo/L	NR	NR/NR	adjusted/RR	1	reference	
					25(0H)D	60–84nmol/L	NR	NR/NR	adjusted/RR	0.94	0.59, 1.47	
					25(0H)D	>84nmol/L	NR	NR/NR	adjusted/RR	0.52	0.32, 0.85	<0.05
					25(0H)D	<60nmo/L-Premenopausal women	NR	NR/NR	adjusted/RR	1	reference	
					25(0H)D	60–84nmol/L-Premenopausal women	NR	NR/NR	adjusted/RR	0.59	0.26, 1.33	
					25(0H)D	>84nmol/L-Premenopausal women	NR	NR/NR	adjusted/RR	0.38	0.15, 0.97	<0.05
					25(0H)D	<60nmo/L-Postmenopausal women	NR	NR/NR	adjusted/RR	1	reference	
					25(0H)D	60–84nmol/L-Postmenopausal women	NR	NR/NR	adjusted/RR	1.2	0.67, 2.16	
					25(0H)D	>84nmol/L-Postmenopausal women	NR	NR/NR	adjusted/RR	0.71	0.38, 1.30	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Rejnmark et al., 2009	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Roth et al., 2013	RCT/CCT	9–18 years; 19–50 years; Pregnant or lactating women; age 18–<35 years; gestational age of 26–<30 weeks; current residence in Dhaka at a fixed address; planned to deliver at the Shimantik maternity center	use of any dietary supplement containing more than 400 IU/ day (10 mcg/day) of vitamin D within the month prior to enrolment, or refusal to stop taking supplemental vitamin D at any dose after enrollment; current use of anticonvulsant or anti-mycobacterial (tuberculosis) medications; severe anemia (hemoglobin < 70 g/L); systolic blood pressure =140 mm Hg or diastolic blood pressure =90 mm Hg; positive urine dipstick for proteinuria or glycosuria; complicated medical or obstetric history; reported prior history of delivery of an infant with a major congenital anomaly, birth asphyxia, or perinatal death	Antenatal Vitamin D in Dhaka (AViDD) trial	Private Foundation	Dhaka, Bangladesh	160/147/100	22.4 (3.5)/NR			Serum 25(OH)D placebo: 44.0 ± 20.9 nmol/l vitamin D: 45.4 ± 18.4 nmol/l

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Roth et al., 2013	RCT/CCT	NR	NR	Secondary-Birth Weight	35000 IU Vit D3 3rd trimester		73	NR (NR)	Final=2802 (2675, 2929)	+14 (-138, 166)	0.86
					Placebo		74	NR (NR)	Final=2788 (2700, 2876)		.
				Secondary-Length At Birth	35000 IU Vit D3 3rd trimester		73	NR (NR)	Final=48.2 (47.6, 48.8)	+0.2 (-0.5, 0.9)	0.55
					Placebo		74	NR (NR)	Final=48 (47.5, 48.5)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Roth et al., 2013	RCT/CCT	Y	Y	N	Y	Y	Y	ND	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Rouzi et al., 2012	Prospective Cohort	19–50 years; 51–70 years; Postmenopausal women; Healthy; age=50 years; independent mobility; unrestricted diet; normal liver, renal function	Osteoporosis; Prior cancer; Current cancer; t-score<-2.5		Government	Jeddah, Saudi Arabia	707/707/100	61.3 (7.2)/NR		Post menopausal	Serum 25(OH)D: 34.27±22.80 nmol/L

ain Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Rouzi et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Smoking, Other Lifestyle Factors- Smoking, Coffee/Tea Consumption; Other - Previous Fractures, Hormone Levels, Bone Turnover Markers	Primary-Fragility Fractures	25(OH)D	<17.90 nmol/L	5.2 yrs	138/707	adjusted/OR	1.25	0.91, 1.70	
					25(OH)D	>45.1 nmol/L	5.2 yrs		adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Rouzi et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Sabetta et al., 2010	Prospective Cohort	Healthy	Current cardiovascular disease; Type 2 DM; Pregnant; chronic pulmonary, renal hepatic, hematologic, neurologic, neuromuscular, or metabolic disorder; immunosuppression; high-dose aspirin therapy		a private family	USA; Greenwich, CT	198/198/57	NR/20–88	Race_other1= 78; Race_other2= 16; Race_other3= 6		Serum vitamin D: 28.4±0.8 ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Sabetta et al., 2010	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Use Of Vitamins Other Than D, Herbals And Other Supplements; Demographics (Age, Sex, Race/Ethnicity)- Sex, Age; Anthropometrics- Skin Pigmentation; Other - Receipt Of Seasonal and/or H1n1 Influenza Vaccine	Primary-Acute Viral Respiratory Tract Infections	25(0H)D	>=38ng/ml	4 months	3/18	Crude/OR	0.24	0.07, 0.87	
					25(0H)D	<38ng/ml	4 months	81/180	Crude/OR	1	reference	0.015

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Sabetta et al., 2010	N	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	Y	Y	A	no inclusion criteria

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Salehpour et al., 2012	RCT/CCT	9–18 years; 19–50 years; Healthy; women; 18–50 years of age; BMI=25kg/m2; free of known osteoporosis, gastrointestinal disease, diabetes mellitus, CVD, renal disease, hypertension	Pregnant; any; On a weight loss program; taking weight loss drugs; weight change of >3kg during the prior 3 months; lactating; smoking; drinking alcohol; taking nutrition supplements, cholesterol or TAG-lowering agents as well as anti-hypertensive agents		university	Tehran, Iran	85/85/100	38 (8.1)/NR		Overweight/obese	S-25(OH)D Vit D group - 36.8 +/- 30 nmol/l Placebo group - 46.9 +/- 32 nmol/l

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Salehpour et al., 2012	RCT/CCT	NR	Other Nutrients Or Dietary Factors- Dietary Intake; Anthropometrics- Fat Mass, Waist Circumference; Smoking, Other Lifestyle Factors- Physical Activity (Not Smoking)	Secondary-DBP	D3 Vit D 25 µg/day		42	67.9 (sd=10.1)	final=70.2 (sd=8.8)	-1.9 (-6.1, 2.3)	.
					D3 placebo		43	71.9 (sd=9.1)	final=72.1 (sd=10.6)		.
				Secondary-SBP	D3 Vit D 25 µg/day		42	110.5 (sd=17.5)	final=111 (sd=11.3)	-3.4 (-8.7, 1.9)	.
					D3 placebo		43	116.7 (sd=11.4)	final=114.4 (sd=13)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Salehpour et al., 2012	RCT/CCT	Y	ND	N	Y	ND	ND	Y	Y	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Salovaara et al., 2010	RCT/CCT	51–70 years; women; Birth between 1932 and 1941; Age 65 and over at current followup; Residence in Northern Savonia		OSTPRE Study	Hospital	Finland	3195/3195/100	67.3 (1.8)/NR		Not Reported	Serum vitamin D: 49.1±17.7 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Salovaara et al., 2010	RCT/CCT	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking, Use Of Alcohol; Other - Parental Hip Fracture, Glucocorticoid Use, Diagnosed Rheumatoid Arthritis, Secondary Osteoporosis	Primary-Any Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	78/1586	adjusted/HR	0.83	0.61, 1.12	
						control (no intervention or placebo)	3.01 yrs	94/1609	adjusted/HR	1	Reference	
				Primary-Any Nonvertebral Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	71/1586	adjusted/HR	0.87	0.63, 1.19	
						control (no intervention or placebo)	3.01 yrs	82/1609	adjusted/HR	1	Reference	
				Primary-Any Osteoporotic Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	42/1586	adjusted/HR	0.81	0.54, 1.22	
						control (no intervention or placebo)	3.01 yrs	52/1609	adjusted/HR	1	Reference	
				Primary-Distal Forearm Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	23/1586	adjusted/HR	0.7	0.41, 1.20	
						control (no intervention or placebo)	3.01 yrs	32/1609	adjusted/HR	1	Reference	
				Primary-Proximal Humerus Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	6/1586	adjusted/HR	1.01	0.32, 3.14	
						control (no intervention or placebo)	3.01 yrs	6/1609	adjusted/HR	1	Reference	
				Primary-Hip Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	4/1586	adjusted/HR	2.23	0.41, 12.29	
						control (no intervention or placebo)	3.01 yrs	2/1609	adjusted/HR	1	Reference	
				Primary-Vertebral Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	9/1586	adjusted/HR	0.67	0.29, 1.58	
						control (no intervention or placebo)	3.01 yrs	13/1609	adjusted/HR	1	Reference	
				Primary-Upper Extremity Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	41/1586	adjusted/HR	0.75	0.49, 1.16	
						control (no intervention or placebo)	3.01 yrs	50/1609	adjusted/HR	1	Reference	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
				Primary-Lower Extremity Fracture	vitamin D; calcium	400 IU cholecalciferol + 500 mg calcium carbonate	3.01 yrs	22/1586	adjusted/HR	1.02	0.58, 1.80	
						control (no intervention or placebo)	3.01 yrs	20/1609	adjusted/HR	1	Reference	

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Salovaara et al., 2010	RCT/CCT	Y	Y	ND	Y	N	Y	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Salzer et al., 2012	Nested Case Control	19–50 years; 51–70 years; Individuals 30, 40, 50, and 60 years of age; women 50–69 years of age; residence in Vasterbotten Sweden; no symptoms of MS prior to blood sampling	Not specified	Risk of Multiple Sclerosis	Manufacturer	Sweden	576/576/92.2	26/16–60	Race_other1= 99; Race_other2= 1	Not Reported	Serum vitamin D: 40nmol/L (range 0–122)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Salzer et al., 2012	Nested Case Control	Sex, biobank, sampling date, age	NR	Primary-Multiple Sclerosis	25(0H)D	>=75nmol/l	NR	192/576	Adjusted/OR	0.39	0.16, 0.98	NR
					25(0H)D	<75nmol/l	NR		Adjusted/OR	1	reference	NR

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Salzer et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	Y	Y	N	N	A	Sampling = Consecutive

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Salzer et al., 2012	Nested Case Control	Pregnant or lactating women	Not specified	Gestational Risk factors of Multiple Sclerosis (GRoMS)	Manufacturer	Sweden	222/222/100	27/19–40			Serum vitamin D: 40nmol/L (0–335)_

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Salzer et al., 2012	Nested Case Control	sex, biobank, sampling date, age	NR	Primary-Multiple Sclerosis	25(0H)D	>=75nmol/l	NR	37/222	Adjusted/OR	1.8	0.53, 5.8	NR
					25(0H)D	<75nmol/l	NR		Adjusted/OR	1	reference	NR

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Salzer et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	Y	Y	N	N	A	Sampling = Consecutive

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Schierbeck et al., 2012	Prospective Cohort	19–50 years; 51–70 years; Postmenopausal women; Healthy; women; Age 45–58; Recently postmenopausal with last menstrual bleeding 3–24 months before enrollment or perimenopausal with elevated FSH; Caucasian	Osteoporosis; Other systemic bone disease (e.g., Paget's); Prior fragility fracture; Prior cancer; Current cancer; Uncontrolled chronic disease, thromboembolic disease; Current or past treatment with glucocorticoids, alcohol or drug addiction; Current or previous post-menopausal hormone therapy in past 3 months	Danish Osteoporosis Prevention Study	University	Denmark	2,013/2013/100	50.0 (2.8)/NR	Non-Hispanic White=100	Post menopausal	Serum 25(OH)D: Low vitamin D group: 35±10 High vitamin D group: 80±26

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Schierbeck et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Education; Anthropometrics- Waist-Hip Ratio; Smoking, Other Lifestyle Factors- Smoking; Other - Family History Of MI, Use Of Menopausal Hormone Therapy Was Not Controlled For But Did Not Differ Between High And Low Vitamin D Groups	Primary-Heart Failure	25(OH)D	<50 nmol/l	16 yrs	10/788	Adjusted/HR	1.88	0.71, 5.01	0.206
					25(OH)D	>=50 nmol/l	16 yrs	8/1225	Adjusted/HR	1	Reference	
				Primary-Myocardial Infarction	25(OH)D	<50 nmol/l	16 yrs	13/788	Adjusted/HR	0.83	0.41, 1.67	0.597
					25(OH)D	>=50 nmol/l	16 yrs	22/1225	Adjusted/HR	1	Reference	
				Primary-Stroke	25(OH)D	<50 nmol/l	16 yrs	47/788	Adjusted/HR	1.68	1.10, 2.56	0.017
					25(OH)D	>=50 nmol/l	16 yrs	42/1225	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Schierbeck et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Scholl et al., 2013	Prospective Cohort	Pregnant or lactating women	Current cancer; Hypertension; Type 2 DM; Autoimmune disease; Type 1 diabetes; seizure disorders; drug or alcohol abuse; other serious non-obstetric conditions	Camden Study	Government	USA; Camden NJ	1,141/1141/100	22.8 (5.4)/NR	Non-Hispanic White=140; Hispanic=513; Non-Hispanic Black=347	Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Scholl et al., 2013	Prospective Cohort	Not relevant	Other Nutrients Or Dietary Factors- Total Calcium Intake; Demographics (Age, Sex, Race/Ethnicity)- Age, Ethnicity; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking; Other - Gestational Stage At Entry	Primary- Preeclampsia	25(OH)D	<30	20 weeks gestation	12/121	adjusted/OR	2.13	1.07, 4.26	0.027
					25(OH)D	30–40	20 weeks gestation	12/116	adjusted/OR	2.09	1.04, 4.22	
					25(OH)D	40–50	20 weeks gestation	7/154	adjusted/OR	0.94	0.41, 2.17	
					25(OH)D	>=50	20 weeks gestation	38/750	adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Scholl et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Schottker et al., 2013	Prospective Cohort	51–70 years; age 50–74 years	Not specified	ESTHER	Government	Germany (specify city, if given)	9578/9578/56.2	62 (6.5)/NR		Not Reported	25(OH)D: 51.1 +/- 24.6 nmol/l

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Schottker et al., 2013	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Regular Intake Of Multivitamin Supplements, Fish Consumption; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Medical Conditions- Chronic Kidney Disease, Diabetes, Hypertension, Cardiovascular Disease, Cancer; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Physical Activity, Smoking; Other - Serum C-Reactive Protein Concentrations, Total Cholesterol	Primary-All-Cause Mortality	25(OH)D	<30	9.5 yrs	238/1444	adjusted/HR	1.68	1.41, 2.01	
					25(OH)D	30–50	9.5 yrs	448/4199	adjusted/HR	1.17	1.01, 1.35	
					25(OH)D	>50	9.5 yrs	397/3935	adjusted/HR	1	reference	
					25(OH)D	<30->=65 years of age	9.5 yrs	142/609	adjusted/HR	1.41	1.13, 1.77	
					25(OH)D	30–50->=65 years of age	9.5 yrs	269/1706	adjusted/HR	1.09	0.90,1.31	
					25(OH)D	>50->=65 years of age	9.5 yrs	236/1394	adjusted/HR	1	reference	
					25(OH)D	<30–<65 years of age	9.5 yrs	238/835	adjusted/HR	2.08	1.58, 2.76	
					25(OH)D	30–50–<65 years of age	9.5 yrs	448/2493	adjusted/HR	1.3	1.04, 1.63	
					25(OH)D	>50–<65 years of age	9.5 yrs	397/2541	adjusted/HR	1	reference	
				Secondary-Cvd Mortality	25(OH)D	<30	9.5 yrs	71/1439	adjusted/HR	1.29	0.94, 1.76	
					25(OH)D	30–50	9.5 yrs	137/4188	adjusted/HR	0.94	0.73, 1.21	
					25(OH)D	>50	9.5 yrs	142/3927	adjusted/HR	1	reference	
				Secondary-Cancer Mortality	25(OH)D	<30	9.5 yrs	90/1439	adjusted/HR	1.42	1.08, 1.87	
					25(OH)D	30–50	9.5 yrs	172/4188	adjusted/HR	1.04	0.83, 1.29	
					25(OH)D	>50	9.5 yrs	171/3927	adjusted/HR	1	reference	
				Secondary-Respiratory Disease Mortality	25(OH)D	<30	9.5 yrs	13/1439	adjusted/HR		NR	
					25(OH)D	30–50	9.5 yrs	26/4188	adjusted/HR		NR	
					25(OH)D	>50	9.5 yrs	16/3927	adjusted/HR	1	reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Schottker et al., 2013	N	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Science et al., 2013	Prospective Cohort	3–8 years; 9–18 years; age 3–15 years	underlying chronic medical conditions		Government	Canada	947/743/52.5	9.3 (3.4)/NR		Not Reported	serum 25(OH)D: median (IQR) 62.0 (51.0–74.0) nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Science et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex	Primary-Respiratory Tract Infections	25(OH)D	per 1-unit change in log levels	156 days	229/743	adjusted/HR	0.52	0.35, 0.79	0.002
					25(OH)D	<25	156 days	NR/4	unadjusted/HR	0.72	0.13, 3.94	0.7
					25(OH)D	>=25	156 days	NR/739	unadjusted/HR	1	Reference	
					25(OH)D	<50	156 days	NR/152	unadjusted/HR	1.54	1.07, 2.21	0.021
					25(OH)D	>=50	156 days	NR/591	unadjusted/HR	1	Reference	
					25(OH)D	<75	156 days	NR/565	unadjusted/HR	1.35	1.01, 1.82	0.043
					25(OH)D	>=75	156 days	NR/178	unadjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Science et al., 2013	Y	N	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Scott et al., 2010	Prospective Cohort	19–50 years; 51–70 years; on electoral rolls in southern Tasmania; community dwelling	institutionalized; contraindications to MRI	Tasmanian Older Adult Cohort Study (TASOAC)	University	Australia; Tasmania	686/686/49	62 (7)/50–79	Non-Hispanic White=98	Not Reported	Serum 25OH(D) Low vitamin D: 37.1±8.4 High vitamin D: 67.8±13.4

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Scott et al., 2010	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Use Of Vitamin D Supplements; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex; Anthropometrics- BMI; Sun Exposure- Self-Reported Sun Exposure And Season Of Blood Draw; Smoking, Other Lifestyle Factors- Physical Activity	Secondary-Appendicular Lean Mass	25(OH)D > 50nmol/l		389	62.20 (SD=9.6)	NR (NR)	+0.01 (-0.52, 0.54)	0.963
					25(OH)D = 50nmol/l		297	59.30 (SD=9.9)	NR (NR)		.
				Secondary-Leg Strength	25(OH)D > 50nmol/l		389	100.80 (SD=50.1)	NR (NR)	+5.74 (0.65, 10.82)	0.027
					25(OH)D = 50nmol/l		297	91.50 (SD=47.8)	NR (NR)		.
				Secondary-Leg Muscle Quality	25(OH)D > 50nmol/l		389	5.90 (SD=2.3)	NR (NR)	+0.49 (0.17, 0.82)	0.003
					25(OH)D = 50nmol/l		297	5.50 (SD=2.3)	NR (NR)		.

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Scott et al., 2010	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	N	N	B	random except stratified by sex loss to follow-up = 20%

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Semba et al., 2010	Prospective Cohort	51–70 years; adults=65 years of age; community dwelling	Not specified	InCHIANTI		Italy	1,006/NR/32.7	78.0/72.0–85.0			

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Semba et al., 2010	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Education; Anthropometrics- BMI; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking, Physical Activity; Other - Blood Lipids, Renal Insufficiency, Mini Mental Status Exam Score	Primary-All-Cause Mortality	25(OH)D	Q1:<26.2 nmol/L	6.5 yrs	nr/NR	adjusted/HR	2.11	1.22, 3.64	NR
					25(OH)D	Q2:26.2–40 nmol/L	6.5 yrs	nr/NR	adjusted/HR	1.41	0.83, 2.40	
					25(OH)D	Q3: 40–63.9 nmol/L	6.5 yrs	nr/NR	adjusted/HR	1.12	1.09, 1.15	
					25(OH)D	Q4: >63.6 nmol/L	6.5 yrs	nr/NR	adjusted/HR	1	reference	
				Primary-Cardiovascular Disease Mortality	25(OH)D	Q1:<26.2 nmol/L	6.5 yrs	nr/NR	adjusted/HR	2.64	1.68, 2.19	NR
					25(OH)D	Q2:26.2–40 nmol/L	6.5 yrs	nr/NR	adjusted/HR	1.68	0.76, 3.72	
					25(OH)D	Q3: 40–63.9 nmol/L	6.5 yrs	nr/NR	adjusted/HR	2.19	1.05, 4.60	
					25(OH)D	Q4: >63.6 nmol/L	6.5 yrs	nr/NR	adjusted/HR	1	reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Semba et al., 2010	N	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	design b- unclear

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Sempos et al., 2013	Prospective Cohort	19–50 years; 51–70 years; age >=20 years	Pregnant; missing information on vital status; missing data for serum total 25(OH)D, serum creatinine, SBP; no follow-up time from data of examination	NHANES III	Government	USA	15099/15099/51	45 (SE=0.47)/NR	Non-Hispanic White=77; Hispanic=5; Non-Hispanic Black=10; Race_other1=8	Not Reported	Serum 25(OH)D 64 nmol/liter (SE 0.73)

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Sempos et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race/Ethnicity; Sun Exposure-Season	Primary-Death From All-Cause	25(OH)D	<20	15 yrs	79/251	adjusted/RR	1.6	1.2, 2.2	
					25(OH)D	20–29	15 yrs	297/1270	adjusted/RR	1.5	1.2, 1.8	
					25(OH)D	30–39	15 yrs	592/2340	adjusted/RR	1.3	1.1, 1.5	
					25(OH)D	40–49	15 yrs	694/2790	adjusted/RR	1.1	0.96, 1.3	
					25(OH)D	50–59	15 yrs	668/2526	adjusted/RR	1.2	1.01, 1.30	
					25(OH)D	60–74	15 yrs	775/3046	adjusted/RR	1.1	0.99, 1.30	
					25(OH)D	75–99	15 yrs	533/2156	adjusted/RR	1	Reference	
					25(OH)D	100–119	15 yrs	110/518	adjusted/RR	1.1	0.9, 1.4	
					25(OH)D	>=120	15 yrs	36/202	adjusted/RR	1.4	0.9, 2.2	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Sempos et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	ref 9: http://www.cdc.gov/nchs/data/series/sr_01/sr01_032.pdf

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Shand et al., 2010	Prospective Cohort	9–18 years; 19–50 years; Pregnant or lactating women; =18 years; 10–20 weeks gestation; increased risk for pre-eclampsia	Not specified	EMMA	none	Canada; Vancouver CA	227/NR/100	NR/NR	Non-Hispanic White=611; Race_other1= 204; Race_other2= 136; Race_other3= 5		

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Shand et al., 2010	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Multivitamin Use; Demographics (Age, Sex, Race/Ethnicity)- Age, Ethnicity; Anthropometrics- BMI; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking Status	Primary- Preeclampsia	25(OH)D	<37.5	10–20 weeks gestation	10/NR	adjusted/OR	0.91	0.31, 2.62	
					25(OH)D	>=37.5	10–20 weeks gestation	18/NR	adjusted/OR	1	Reference	
					25(OH)D	<50	10–20 weeks gestation	17/NR	adjusted/OR	1.39	0.54, 3.53	
					25(OH)D	>=50	10–20 weeks gestation	11/NR	adjusted/OR	1	Reference	
					25(OH)D	<75	10–20 weeks gestation	21/NR	adjusted/OR	0.57	0.19, 1.66	
					25(OH)D	>=75	10–20 weeks gestation	6/NR	adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Shand et al., 2010	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Shin et al., 2013	Prospective Cohort	Pregnant or lactating women	diabetes; preeclampsia; anemia; severe infections during pregnancy	COhort for Childhood Origin of Asthma and allergic diseases (COCOA)	Government	Korea	1545/525/mothers: 100, newborns: 46.9	maternal age: 32.2 (maternal age: 3.4)/newborns: 0–6 months		Not Reported	mean cord blood plasma 25(OH)D 32.0 nmol/L (IQR, 21.4 to 53.2)

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Shin et al., 2013	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Multivitamin Use During Pregnancy; Sun Exposure- Season Of Birth; Smoking, Other Lifestyle Factors- Exposure To Passive Smoking During Pregnancy	Primary-Respiratory Tract Infections	25(OH)D	<25.0	6 months	74/180	adjusted/OR	3.41	1.57, 7.42	0.0008
					25(OH)D	25.0–74.9	6 months	89/292	adjusted/OR	2.14	1.00, 4.58	
					25(OH)D	>=75.0	6 months	9/53	adjusted/OR	1	Reference	
				Primary-Acute Nasopharyngitis	25(OH)D	<25.0	6 months	67/180	adjusted/OR	4.64	1.88, 11.44	0.0002
					25(OH)D	25.0–74.9	6 months	75/292	adjusted/OR	2.71	1.11, 6.59	
					25(OH)D	>=75.0	6 months	6/53	adjusted/OR	1	Reference	
				Primary-Otitis Media	25(OH)D	<25.0	6 months	10/180	adjusted/OR	3.06	0.38, 24.46	0.3625
					25(OH)D	25.0–74.9	6 months	18/292	adjusted/OR	3.42	0.45, 26.15	
					25(OH)D	>=75.0	6 months	1/53	adjusted/OR	1	Reference	
				Primary-Bronchiolitis	25(OH)D	<25.0	6 months	9/180	adjusted/OR	2.74	0.34, 22.11	0.4819
					25(OH)D	25.0–74.9	6 months	19/292	adjusted/OR	3.62	0.47, 27.63	
					25(OH)D	>=75.0	6 months	1/53	adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Shin et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Shui et al., 2012	Nested Case Control	US male health professionals aged 40–75 in 1986; provided chilled blood sample between 1993 and 1995; For controls, PSA test within 2.5 years of date of diagnosis of matched case	cases with T1a tumors	Health Professionals' Follow-up Study	Private Foundation	USA	2,591/2584/0	64.4 (7.8)/NR	Non-Hispanic White=95; Not reported=5	Not Reported	NR

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Shui et al., 2012	Nested Case Control	age, PSA test before blood collection, time (of day) of blood collection, season of blood collection, year	Other Nutrients Or Dietary Factors- Energy Adjusted Lycopene And Calcium Intakes, Total Energy Intake, Red Meat Servings Per Week, Fish Servings Per Week; Demographics (Age, Sex, Race/Ethnicity)- Age, Race; Anthropometrics- BMI, Height; Medical Conditions- Type 2 Diabetes Status; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking, Coffee Intake, Vigorous Physical Activity; Other - Follow-Up Time, Family History Of Prostate Cancer, Vasectomy Status	Primary-Lethal Prostate Cancer	25(0H)D	Quartile 1	5.2 years	41/366	adjusted/OR	1	reference	
					25(0H)D	Quartile 2	5.2 years	33/369	adjusted/OR	0.78	0.47, 1.30	
					25(0H)D	Quartile 3	5.2 years	21/335	adjusted/OR	0.5	0.28, 0.88	
					25(0H)D	Quartile 4	5.2 years	19/348	adjusted/OR	0.44	0.24, 0.79	0.002
				Primary-Overall Prostate Cancer	25(0H)D	Quartile 1	5.2 years	310/635	adjusted/OR	1	reference	
					25(0H)D	Quartile 2	5.2 years	298/634	adjusted/OR	0.93	0.74, 1.17	
					25(0H)D	Quartile 3	5.2 years	319/653	adjusted/OR	0.99	0.79,1.24	
					25(0H)D	Quartile 4	5.2 years	333/662	adjusted/OR	1.07	0.86, 1.34	0.450
				Primary-Advance Stage At Diagnosis	25(0H)D	Quartile 1	5.2 years	51/376	adjusted/OR	1	reference	
					25(0H)D	Quartile 2	5.2 years	43/379	adjusted/OR	0.96	0.61, 52	
					25(0H)D	Quartile 3	5.2 years	32/366	adjusted/OR	0.63	0.39, 1.03	
					25(0H)D	Quartile 4	5.2 years	40/662	adjusted/OR	0.85	0.53,1.35	0.220
				Primary-High Grade Prostate Cancer	25(0H)D	Quartile 1	5.2 years	69/394	adjusted/OR	1	reference	
					25(0H)D	Quartile 2	5.2 years	55/391	adjusted/OR	0.81	0.54, 1.21	
					25(0H)D	Quartile 3	5.2 years	51/385	adjusted/OR	0.75	0.50, 1.13	
					25(0H)D	Quartile 4	5.2 years	64/393	adjusted/OR	0.99	0.67, 1.46	0.870

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Shui et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	very minimal eligibility criteria

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Signorello et al., 2013	Prospective Cohort	19–50 years; 51–70 years; 40–79 years of age; English speaking; No cancer treatment within the previous year	Not specified	Southern Community Cohort Study	Government	USA	3,704/3704/NR	NR/NR	Non-Hispanic White=27; Non-Hispanic Black=69; Not reported=4	Not Reported	NR

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Signorello et al., 2013	Prospective Cohort	sex, race, age at enrollment, enrollment site, date of blood collection	Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking Status, Total Physical Activity	Primary-All-Cause Mortality	25(OH)D	Quartile 4: (>21.64 ng/mL)	NR	364/827	adjusted/OR	1	Reference	<0.001
					25(OH)D	Quartile 3: (15.16–21.64 ng/mL)	NR	405/868	adjusted/OR	1.17	0.95, 1.45	
					25(OH)D	Quartile 2: (10.18–15.15 ng/mL)	NR	482/945	adjusted/OR	1.41	1.14, 1.74	
					25(OH)D	Quartile 1: <10.18 ng/mL)	NR	601/1064	adjusted/OR	1.8	1.43, 2.27	
					25(OH)D	Quartile 4: (>21.64 ng/mL)-African Americans	NR	181/400	adjusted/OR	1	Reference	0.003
					25(OH)D	Quartile 3: (15.16–21.64 ng/mL)-African Americans	NR	266/565	adjusted/OR	1.15	0.87, 1.53	
					25(OH)D	Quartile 2: (10.18–15.15 ng/mL)-African Americans	NR	353/730	adjusted/OR	1.19	0.91, 1.57	
					25(OH)D	Quartile 1: <10.18 ng/mL)-African Americans	NR	475/855	adjusted/OR	1.6	1.20, 2.14	
					25(OH)D	Quartile 4: (>21.64 ng/mL)-non African Americans	NR	179/419	adjusted/OR	1	Reference	<0.001
					25(OH)D	Quartile 3: (15.16–21.64 ng/mL)-non African Americans	NR	136/296	adjusted/OR	1.09	0.78, 1.52	
					25(OH)D	Quartile 2: (10.18–15.15 ng/mL)-non African Americans	NR	129/214	adjusted/OR	1.99	1.37, 2.90	
					25(OH)D	Quartile 1: <10.18 ng/mL)-non African Americans	NR	122/203	adjusted/OR	2.11	1.39, 3.21	
				Primary-Cancer Death	25(OH)D	Quartile 4: (>21.64 ng/mL)	NR	115/228	adjusted/OR	1	Reference	0.53
					25(OH)D	Quartile 3: (15.16–21.64 ng/mL)	NR	102/228	adjusted/OR	0.79	0.52, 1.21	
					25(OH)D	Quartile 2: (10.18–15.15 ng/mL)	NR	127/255	adjusted/OR	1.03	0.66, 1.59	
					25(OH)D	Quartile 1: <10.18 ng/mL)	NR	133/243	adjusted/OR	1.28	0.78, 2.11	
				Primary-Circulatory Disease Death	25(OH)D	Quartile 4: (>21.64 ng/mL)-African Americans	NR	41/109	adjusted/OR	1	Reference	0.01
					25(OH)D	Quartile 3: (15.16–21.64 ng/mL)-African Americans	NR	76/162	adjusted/OR	1.67	0.95, 2.93	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
					25(OH)D	Quartile 2: (10.18–15.15 ng/mL)-African Americans	NR	116/225	adjusted/OR	1.78	1.05, 3.01	
					25(OH)D	Quartile 1: <10.18 ng/mL)-African Americans	NR	144/258	adjusted/OR	2.53	1.44, 4.46	
					25(OH)D	Quartile 4: (>21.64 ng/mL)-non African Americans	NR	40/107	adjusted/OR	1	Reference	0.01
					25(OH)D	Quartile 3: (15.16–21.64 ng/mL)-non African Americans	NR	38/84	adjusted/OR	1.09	0.51. 2.30	
					25(OH)D	Quartile 2: (10.18–15.15 ng/mL)-non African Americans	NR	37/56	adjusted/OR	3.66	1.50, 8.95	
					25(OH)D	Quartile 1: <10.18 ng/mL)-non African Americans	NR	39/61	adjusted/OR	3.25	1.33, 7.93	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Signorello et al., 2013	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Simpson et al., 2011	Prospective Cohort	0–6 months; 7 months–2 years; 3–8 years; birth to 8 years of age at recruitment; born at St. Joseph's Hospital in Denver CO; positive for diabetes-susceptibility alleles in the HLA region	Not specified	Diabetes Autoimmunity Study in the Young (DAISY)	Private Foundation	USA; Denver CO	185/185/51	11.9 (4.4)/NR	Non-Hispanic White=76	Other; at increased risk for Type 1 diabetes	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Simpson et al., 2011	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Ethnicity; Other - HLA Genotype,, Age At First Islet Autoimmunity Positivity	Primary-Islet Autoimmune (IA)	25(0H)D; 9months	Inadequate (<=50nmol/L vs adequate)-Study 1c	NR	30/128	Adjusted/HR	0.72	0.24, 2.17	0.56
				Primary-Type 1 Diabetes In IA Positive	25(0H)D	Inadequate (<=50nmol/L vs adequate)-Study 2b	NR	55/185	Adjusted/HR	0.44	0.14, 1.45	0.18

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Simpson et al., 2011	Y	Y	Y	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Skaaby et al., 2013	Prospective Cohort	19–50 years; 51–70 years; age 30–71 years	Not specified	Monica10 and Inter99	Private Foundation	Denmark	2649 (Monica10), 6497 (Inter99)/8329/ 49.8 (Monica10), 50.8 (Inter99)	55.4 (Monica10), 46.1 (Inter99)/41.0–72.8 (Monica10), 29.7–61.3 (Inter99)		Not Reported	Median vitamin D 61.0 nmol/l, interquartile range 44.7–80.9 nmol/l (Monica10); median 48.0 nmol/l, interquartile range 32.0–65.0 nmol/l (Inter99).

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Skaaby et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Gender; Medical Conditions- Body Mass Index; Sun Exposure- Season Of Blood Sample; Smoking, Other Lifestyle Factors- Intake Of Fish, Physical Activity, Smoking Habits, Alcohol Consumption; Other - Education	Primary-Ischemic Heart Disease	25(OH)D	per 10nmol/L	10 yrs	478/8131	adjusted/HR	1.01	0.98, 1.05	0.44
					25(OH)D	Q1	10 yrs		adjusted/HR	1	reference	0.25
					25(OH)D	Q2	10 yrs		adjusted/HR	1.17	0.91, 1.51	
					25(OH)D	Q3	10 yrs		adjusted/HR	1	0.76, 1.31	
					25(OH)D	Q4	10 yrs		adjusted/HR	1.24	0.95, 1.62	
				Primary-Stroke	25(OH)D	per 10nmol/L	10 yrs	316/8131	adjusted/HR	1	0.96, 1.05	0.92
					25(OH)D	Q1	10 yrs		adjusted/HR	1	reference	0.78
					25(OH)D	Q2	10 yrs		adjusted/HR	1.08	0.79, 1.49	
					25(OH)D	Q3	10 yrs		adjusted/HR	1.18	0.86, 1.63	
					25(OH)D	Q4	10 yrs		adjusted/HR	1.13	0.80, 1.59	
				Primary-All-Cause Mortality	25(OH)D	per 10nmol/L	10 yrs	633/8329	adjusted/HR	0.95	0.92, 0.99	0.005
					25(OH)D	Q1	10 yrs		adjusted/HR	1	reference	0.041
					25(OH)D	Q2	10 yrs		adjusted/HR	0.79	0.64, 0.98	
					25(OH)D	Q3	10 yrs		adjusted/HR	0.81	0.65, 1.01	
					25(OH)D	Q4	10 yrs		adjusted/HR	0.73	0.57, 0.92	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Skaaby et al., 2013	Y	Y	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Smit et al., 2012	Prospective Cohort	51–70 years; age >=60; non-institutionalized; complete data on frailty; complete data on serum vitamin D concentrations	Not specified		Government	USA; multiple	4731/NR/53.5	69.4 (0.3)/NR	Non-Hispanic White=878; Non-Hispanic Black=60; Race_other1= 17; Race_other2= 45	Malnourished/frailty; Other; pre-frail, not frail	not frail: 71.9 ± 0.9 nmol/l pre-frail: 65.6 ± 1.1 nmol/l frail: 60.4 ± 2.3 nmol/l

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Smit et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Race-Ethnicity, Gender, Education; Anthropometrics- BMI; Medical Conditions- Chronic Disease Index; Sun Exposure- Latitude; Smoking, Other Lifestyle Factors- Smoking	Primary-Mortality	25(OH)D	Quartile 1: <49.5 nmol/l-frail	12 yrs	NR/NR	adjusted/HR	2.98	2.01, 4.42	
					25(OH)D	Quartile 2: 49.5–66.4 nmol/l-frail	12 yrs	NR/NR	adjusted/HR	2.37	1.44, 3.89	
					25(OH)D	Quartile 3: 66.5–84.1 nmol/l-frail	12 yrs	NR/NR	adjusted/HR	2.5	1.48, 4.21	
					25(OH)D	Quartile 4: >84.1 nmol/l-frail	12 yrs	NR/NR	adjusted/HR	1.43	0.83, 2.46	
					25(OH)D	Quartile 1: <49.5 nmol/l-pre-frail	12 yrs	NR/NR	adjusted/HR	1.97	1.61, 2.40	
					25(OH)D	Quartile 2: 49.5–66.4 nmol/l-pre-frail	12 yrs	NR/NR	adjusted/HR	1.62	1.29, 2.03	
					25(OH)D	Quartile 3: 66.5–84.1 nmol/l-pre-frail	12 yrs	NR/NR	adjusted/HR	1.51	1.16, 1.97	
					25(OH)D	Quartile 4: >84.1 nmol/l-pre-frail	12 yrs	NR/NR	adjusted/HR	1.82	1.41, 2.35	
					25(OH)D	Quartile 1: <49.5 nmol/l-not frail	12 yrs	NR/NR	adjusted/HR	1.25	0.97, 1.60	
					25(OH)D	Quartile 2: 49.5–66.4 nmol/l-not frail	12 yrs	NR/NR	adjusted/HR	1.2	0.96, 1.49	
					25(OH)D	Quartile 3: 66.5–84.1 nmol/l-not frail	12 yrs	NR/NR	adjusted/HR	1.11	0.88, 1.40	
					25(OH)D	Quartile 4: >84.1 nmol/l-not frail	12 yrs	NR/NR	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Smit et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Solomon et al., 2010	Nested Case Control	Pooled nested case-control study included data from the following cohort studies: the ATBC Study; CLUE; NYU-WHS; MEC; PLCO; SWHS and SMHS.	Not specified	Cohort Consortium Vitamin D Pooling Project of Rarer Cancers	Government	Multiple Countries	2285/2282/33.5	median: 62 (controls)/IQR: 57–67 (controls	Non-Hispanic White=821; Non-Hispanic Black=42; Asian=100; Race_other1=26	Not Reported	<37.5 nmol/L 25(OH)D - cases: 19.3%, controls: 27.5% <25 nmol/L 25(OH)D - cases: 12.1%, controls: 10.6%

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Solomon et al., 2010	Nested Case Control	age, race/ethnicity, sex, cohort, and date of blood draw	Demographics (Age, Sex, Race/Ethnicity)- Age, Race/Ethnicity, Sex; Anthropometrics- BMI; Medical Conditions- Diabetes; Sun Exposure-; Smoking, Other Lifestyle Factors- Smoking; Other - Date Of Blood Draw	Primary-Pancreatic Cancer	25(0H)D	<25nmol/L	NR	115/256	adjusted/OR	1	reference	
					25(0H)D	25<37.5nmol/L	NR	164/389	adjusted/OR	1.04	0.74, 1.44	
					25(0H)D	37.5<50.0nmol/L	NR	208/494	adjusted/OR	1.1	0.79, 1.55	
					25(0H)D	50.0<75.0nmol/L	NR	306/764	adjusted/OR	1.06	0.76, 1.48	
					25(0H)D	75.0<100.0nmol/L	NR	120/310	adjusted/OR	1.08	0.73, 1.59	
					25(0H)D	<=100nmol/L	NR	39/69	adjusted/OR	2.24	1.22, 4.12	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Solomon et al., 2010	Y	Y	Y	Y				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Sorensen et al., 2012	Nested Case Control	gave birth in Norway between 1992 and 1994; n available serum sample of sufficient quality for 25-OH D analysis	Not specified		Government	Norway	328/328/49	9.0 (3.6)/NR		Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Sorensen et al., 2012	Nested Case Control	NR	Demographics (Age, Sex, Race/Ethnicity)- Sex; Sun Exposure- Season Of Blood Sample	Primary-Type 1 Diabetes	25(0H)D	<=54nmol/L-Offspring of pregnant women	NR	39/94	Adjusted/OR	2.38	1.12, 5.07	
					25(0H)D	>54 and <=59nmol/L-Offspring of pregnant women	NR	31/88	Adjusted/OR	1.78	0.85, 3.74	
					25(0H)D	>69nmol/L and 89nmol/L-Offspring of pregnant women	NR	22/75	Adjusted/OR	1.35	0.63, 2.89	
					25(0H)D	>89nmol/L-Offspring of pregnant women	NR	17/71	Adjusted/OR	1	reference	0.031

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Sorensen et al., 2012	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	N	Y	B	1st reviewer comment for grade C: No sample size calculation, rationale for model (or factors controlled for), no information on blinding

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Suila et al., 2012	RCT/CCT	born at term; birth weight appropriate for gestational age	Not specified		Government	Finland; Helsinki	113/82/50	birth/NR		Not Reported	53 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Suila et al., 2012	RCT/CCT	NR	Other - Gender	Secondary-Cortical Bone Density	D3 Vit D3 1600 IU/day		29	NR (NR)	final=716 (se=7)	-8 (-12.1,-3.9)	.
					D3 Vit D3 1200 IU/day		28	NR (NR)	final=726 (se=7)	+2 (-2.1, 6.1)	0.34
					D3 Vit D3 400 IU/day		25	NR (NR)	final=724 (se=8)		.
				Secondary-Total And Trabecular Bone Density	D3 Vit D3 1600 IU/day		29	NR (NR)	final=430 (se=12)	-18 (-25, -11)	.
					D3 Vit D3 1200 IU/day		28	NR (NR)	final=451 (se=12)	+3 (-4, 10)	0.39
					D3 Vit D3 400 IU/day		25	NR (NR)	final=448 (se=13)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Suila et al., 2012	RCT/CCT	Y	ND	ND	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Sun et al., 2012	Nested Case Control	19–50 years; 51–70 years; female; registered nurses; aged 30–55	Missing 25(OH)D data	Nurses' Health Study	Government	USA; multiple	928/928/100	60.8 (5.9)/NR	Non-Hispanic White=976		Cases- 55.0(25.5) nmol/L; Control-56.8(22.7) nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Sun et al., 2012	Nested Case Control	date and age at blood draw, menopausal status, use of postmenopausal hormone, race, smoking status	Anthropometrics- BMI; Medical Conditions- History Of Chronic Conditions, High Cholesterol; Smoking, Other Lifestyle Factors- Physical Activity, Smoking, Alcohol Consumption; Other - EGFR, C-Reactive Protein	Primary-Ischemic Stroke	25(OH)D	9.2–45.7 nmol/l	17 yrs	171/325	Adjusted/HR	1.49	1.01, 2.18	0.04
					25(OH)D	45.8–65.4 nmol/l	17 yrs	160/314	Adjusted/HR	1.26	0.89, 1.79	
					25(OH)D	66.5–264.3 nmol/l	17 yrs	133/289	Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Sun et al., 2012	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Szulc et al., 2009	Prospective Cohort	51–70 years; men; age 50–85	none	MINOS study	Manufacturer	Montceau les Mines, France	782/782/0	64 (7)/NR		Not Reported	

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Szulc et al., 2009	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Vitamin D Supplementation; Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Medical Conditions- Health Status; Smoking, Other Lifestyle Factors- Smoking, Physical Performance And Activity	Primary-Mortality	25(OH)D	per SD decrease	10 yrs	600/782	adjusted/HR	1.22	1.01, 1.48	
					25(OH)D	Quartile 1 <65 nmol/l summer or <40 nmol/l other months	10 yrs	NR/NR	adjusted/HR	1.44	1.03, 2.03	
					25(OH)D	Quartiles 2–4	10 yrs	NR/NR	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Szulc et al., 2009	Y	Y	Y	Y				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Szulc et al., 2009	Prospective Cohort	51–70 years; men; age 50–85 years	Not specified	MINOS study	Unclear	Montceau les Mines, France	681/NR/0	64 (7)/NR		Not Reported	25(OH)D alive: 70.8 ± 28.8 nM deceased: 57.5 ± 27.5 nM

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Szulc et al., 2009	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Medical Conditions- History Of Ischemic Heart Disease, Arterial Hypertension, Stroke, Parkinson's Disease, Diabetes Mellitus, Pulmonary Diseases, Gastrointestinal And Liver Diseases, Prostate Cancer; Smoking, Other Lifestyle Factors- Smoking, Alcohol Intake, Professional Physical Activity, Leisure Physical Activity, Physical Performance Score; Other - Aortic Calcification Score (ACS), Serum 17be2	Primary-Mortality	25(OH)D	Quartile 1	10 yrs	NR/NR	adjusted/HR		NR	<0.05
					25(OH)D	Quartiles 2–4	10 yrs	NR/NR	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Szulc et al., 2009	Y	Y	Y	N				Y	N	N

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	Y	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Thornton et al., 2013	Prospective Cohort	3–8 years; 9–18 years; age 5–12 years; enrolled in the public primary school system	Not specified	Bogotá School Children Cohort	Unclear	Bogota, Columbia	475/475/52	8.9 (1.6)/NR		Other; ~7–12.5% stunted	25(OH)D: 73.2 ± 19.8 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Thornton et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex	Primary-Earache/Discharge With Fever	25(OH)D	Deficient: <50	140 days	nr/48	adjusted/RR	2.36	1.26, 4.44	
					25(OH)D	Insufficient: 50–<75	140 days	nr/222	adjusted/RR	0.35	0.19, 0.65	
					25(OH)D	Sufficient: >=75	140 days	nr/205	adjusted/RR	1	Reference	
				Primary-Cough With Fever	25(OH)D	Deficient: <50	140 days	nr/48	adjusted/RR	0.77	0.57, 1.04	
					25(OH)D	Insufficient: 50–<75	140 days	nr/222	adjusted/RR	0.53	0.44, 0.65	
					25(OH)D	Sufficient: >=75	140 days	nr/205	adjusted/RR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Thornton et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	Y	NA	Y	N	N	B	Outcome c) primary outcome changed to NA

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Tolppanen et al., 2013	Prospective Cohort	3–8 years; 9–18 years; children from the single and twin births from pregnant women expected to give birth between 1 April 1991 and 31 December 1992; women (mothers) had to be resident in Avon while pregnant, those who left shortly after enrollment were omitted from further follow-up	Not specified	Avon Longitudinal Study of Parents and Children	Government	UK; South West England	14,062/3323/47.9	9.84 (SE: 0.02)/NR	Non-Hispanic White=936; Race_other1=65	Not Reported	serum 25OHD3: 24.9 ng/ml (SE: 0.01) serum 25OHD2: 1.4 ng/ml (IQR: 0.5–2.8)

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Tolppanen et al., 2013	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Serum Concentrations Of Other Hormones Or Metabolites That Are Related To Vitamin D Homeostasis; Demographics (Age, Sex, Race/Ethnicity)- Ethnicity; Anthropometrics- BMI; Sun Exposure- Season, Time Spent Outdoors During Summer, Protection From Ultraviolet B Exposure; Other - Head Of Household Social Class, Mother's And Partner's Education	Primary-Wheezing	25(OH)D2	per doubling of exposure	1 yrs	141/3323	adjusted/OR	0.83	0.68, 1.00	
					25(OH)D3	per doubling of exposure	1 yrs	141/3323	adjusted/OR	1.14	1.03, 1.28	
				Primary-Asthma	25(OH)D2	per doubling of exposure	1 yrs	464/3323	adjusted/OR	0.89	0.78, 1.02	
					25(OH)D3	per doubling of exposure	1 yrs	464/3323	adjusted/OR	1.02	0.93, 1.12	
				Primary-Flexural Dermatitis	25(OH)D2	per doubling of exposure	1 yrs	300/3748	adjusted/OR	0.83	0.72, 0.94	
					25(OH)D3	per doubling of exposure	1 yrs	300/3748	adjusted/OR	1.09	1.00, 1.18	
				Primary-Fvc	25(OH)D2	per doubling of exposure	15 yrs	NR/NR	adjusted/SD change in outcome	0.04	0.00, 0.09	
					25(OH)D3	per doubling of exposure	15 yrs	NR/NR	adjusted/SD change in outcome	0	-0.03, 0.03	
				Primary-Fev	25(OH)D2	per doubling of exposure	15 yrs	NR/NR	adjusted/SD change in outcome	0.06	0.01, 0.10	
					25(OH)D3	per doubling of exposure	15 yrs	NR/NR	adjusted/SD change in outcome	0	-0.03, 0.03	
				Primary-Fef	25(OH)D2	per doubling of exposure	15 yrs	NR/NR	adjusted/SD change in outcome	0	-0.01, 0.01	
					25(OH)D3	per doubling of exposure	15 yrs	NR/NR	adjusted/SD change in outcome		-0.01, 0.00	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Tolppanen et al., 2013	Y	Y	Y	N				Y	N	

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	N	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Tomson et al., 2013	Prospective Cohort	19–50 years; 51–70 years; non-industrial Civil Servants; male; age 40–64 years	Not specified	Whitehall study	Private Foundation	UK; London	5409/5409/0	76.9 (4.9)/NR		Other; self-reported health good/excellent 77.4%	median 25(OH)D 56 nmol/l

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Tomson et al., 2013	Prospective Cohort	NR	Anthropometrics- Body Mass Index,; Medical Conditions- Recall Of A Diagnosis Of Ischaemic Heart Disease, Stroke, Cancer, Or Diabetes, Plus Self-Reported Health/Frailty; Smoking, Other Lifestyle Factors- Smoking Status, Drinking Status; Other - LDL-C, HDL-C, Apolipoprotein A1, Apolipoprotein B, And Blood Pressure, Albumin, Fibrinogen, And C-Reactive Protein, Estimated Glomerular Filtration Rate	Primary-Death, Ischemic Heart Disease	25(OH)D	Doubling Concentration	13.1 yrs	659/5409	adjusted/HR	0.84	0.70, 1.02	
				Primary-Death, Stroke	25(OH)D	Doubling Concentration	13.1 yrs	378/5409	adjusted/HR	0.81	0.63, 1.03	
				Primary-Death, Other Vascular	25(OH)D	Doubling Concentration	13.1 yrs	321/5409	adjusted/HR	0.71	0.54, 0.93	
				Primary-Death, All Vascular	25(OH)D	Doubling Concentration	13.1 yrs	1358/5409	adjusted/HR	0.8	0.70, 0.91	
				Primary-Death, Cancer	25(OH)D	Doubling Concentration	13.1 yrs	809/5409	adjusted/HR	0.84	0.71, 1.00	
				Primary-Death, All Non-Vascular	25(OH)D	Doubling Concentration	13.1 yrs	1857/5409	adjusted/HR	0.77	0.69, 0.86	
				Primary-Death, All Causes	25(OH)D	Doubling Concentration	13.1 yrs	3215/5409	adjusted/HR	0.78	0.72, 0.85	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Tomson et al., 2013	Y	N	N	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	N	Y	N	NA	Y	N	N	B	should get references 21, 22 to check eligibility and sampling --- Outcome c) primary outcome changed to NA Grade changed from C to B

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Toxqui et al., 2013	RCT/CCT	9–18 years; 19–50 years; Healthy; 18–35 years old; non-smoking; non-pregnant; non-breastfeeding	iron metabolism related diseases; amenorrhea; menopause; chronic gastritis, renal disease or blood donor status; allergy to dairy components		Government	Spain	165/109/100	26.5 (3.8)/NR	Non-Hispanic White=100		Serum: D-placebo 62.9 ± 20.8 nmol/L D-fortified 62.3 ± 20.8 nmol/L

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Toxqui et al., 2013	RCT/CCT	NR	NR	Secondary-Systolic Blood Pressure	D 200 IU/day		55	109.3 (sd=10.4)	final=105.9 (sd=9.1)	-2.4 (-5.9, 1.1)	0.178
					D placebo		54	107.7 (sd=11.7)	final=108.3 (sd=9.4)		.
				Secondary-Diastolic Blood Pressure	D 200 IU/day		55	67.1 (sd=8.3)	final=66.6 (sd=7.3)	-0.1 (-2.9, 2.7)	0.944
					D placebo		54	69.2 (sd=9.4)	final=66.7 (sd=7.5)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Toxqui et al., 2013	RCT/CCT	ND	ND	ND	Y	ND	N	Y	N	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Travis et al., 2009	Nested Case Control	19–50 years; 51–70 years; center-specific criteria	Not specified	European Prospective Investigation into Cancer and Nutrition (EPIC)	Government	Multiple Countries	1404/1404/0	60.5 (6.2)/NR		Not Reported	Serum 25OHD controls: 53.5 nmol/L, 95% CI (51.9, 55.1) cases: 53.6 nmol/L, 95% CI (52.0, 55.3)

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Travis et al., 2009	Nested Case Control	study center, age at enrollment (66months), time of day of blood collection (61 hour), and time between blood draw and last consumption of food or drink (<3, 3–6,>6 hours; for Umea, Sweden <4, 4–8, >8 hours)	Demographics (Age, Sex, Race/Ethnicity)- Education; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking Status, Alcohol Intake, Physical Activity	Primary-Prostate Cancer	25(0H)D	Quintile 1 (2.5–40.4nmol/L)	4.1 years	125/276	adjusted/OR	1	reference	
					25(0H)D	Quintile 2(40.5–50.4 nmol/L)	4.1 years	143/293	adjusted/OR	1.27	0.89, 1.81	
					25(0H)D	Quintile 3(50.5–59.1nmol/L)	4.1 years	128/279	adjusted/OR	1.23	0.85, 1.76	
					25(0H)D	Quintile 4 (59.2–70.8nmol/L)	4.1 years	114/269	adjusted/OR	1.06	0.73, 1.55	
					25(0H)D	Quintile 5(70.9–163.7nmol/L)	4.1 years	142/292	adjusted/OR	1.28	0.88, 1.88	
					25(0H)D	Doubling Concentration	4.1 years	652/1404	adjusted/OR	1.17	0.93, 1.47	0.188

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Travis et al., 2009	Y	Y	Y	Y				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Virtanen et al., 2011	Prospective Cohort	51–70 years	Current cancer; Current cardiovascular disease; those without information on stroke history; those without data on serum 25(OH)D	Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study	Government	Finland	1136/1136/51.4	61.8 (6.2)/53.4–72.7		Post menopausal; Other; 54–62% hypertension	Serum 25OHD: 43.7 ± 17.8 nmol/L

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Virtanen et al., 2011	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Education Years; Anthropometrics- BMI; Medical Conditions- Diabetes, Treated Hypertension; Smoking, Other Lifestyle Factors- Smoking; Other - Medication For Hyperlipidemia	Primary-Mortality	25(OH)D	Tertile 1: 8.9–34.0 nmol/L	9.1 yrs	39/379	adjusted/HR	2.06	1.12, 3.80	0.02
					25(OH)D	Tertile 2: 34.1–50.8 nmol/L	9.1 yrs	31/378	adjusted/HR	1.68	0.92, 3.07	
					25(OH)D	Tertile 3: 50.9–112.8 nmol/L	9.1 yrs	17/379	adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Virtanen et al., 2011	Y	Y	N	Y				N	Y	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Wagner et al., 2013	RCT/CCT	Pregnant or lactating women; age 16 years or greater; confirmed singleton pregnancy of less than 16 weeks; intent to receive prenatal care throughout pregnancy	Other systemic bone disease (e.g., Paget's); requirement for chronic diuretic or cardiac medication; active thyroid disease		Private Foundation	USA	504/1008/100	27/18–41	Non-Hispanic White=327; Hispanic=409; Non-Hispanic Black=255; Not reported=09		61.5 nmol/L

Main Analyses (Dichotomous Outcomes)												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event / N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Wagner et al., 2013	RCT/CCT	Not relevant	Demographics (Age, Sex, Race/Ethnicity)- Race	Primary-	D3	2000 IU	NR	9/201	unadjusted/RR	0.55	0.22, 1.34	0.43
					D3	4000 IU	NR	4/193	unadjusted/RR	0.25	0.08, 0.80	0.05
						control	NR	9/110	unadjusted/RR	1	reference	

Main Analyses (Continuous Outcomes)											
Author,Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Wagner et al., 2013	RCT/CCT	Not relevant	Demographics (Age, Sex, Race/Ethnicity)- Race	Secondary-Neonatal Birth Weight	D3 2000 IU		201	( )	final=3382 (sd=759)	+149 (-21, 319)	0.09
					D3 4000 IU		193	( )	final=3231 (sd=632)	-2 (-154, 150)	0.98
					control		110	( )	final=3233 (sd=668)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Wagner et al., 2013	RCT/CCT	N	Y	NA	N	Y	N	Y	Y	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Wamberg et al., 2013	RCT/CCT	9–18 years; 19–50 years; Healthy; age 18–50 years; BMI>30; plasma 25(OH) vitamin D<50 nmol/L	Type 2 DM; fasting plasma glucose>7,; hypercalcemia; impaired renal function (plasma creatinine>130umol/L; impaired hepatic function (alanine aminotransferase >135U/L; history of sarcoidosis, nephrolithiasis, osteomalacia; alcohol or other substance abuse; recent major weight changes,(+/-3 kg) or body weight>125 kg; vitamin D treatment within prior 3 months		Unclear	Denmark	52/43/73	41.2 (6.8)/18–50		Overweight/obese	34.6±10.3 nmol/L

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Wamberg et al., 2013	RCT/CCT	Not relevant but arms were balanced with respect to sex, age, bod weight, BMI, blood pressure, fasting glucose, physical activity, dietary baseline vitamin D intake, and plasma 25(OH)D.	NR	Secondary-Systolic Blood Pressure	D 7000 IU cholecalciferol		22	135 (sd=18)	final=129 (sd=13)	-2 (-11, 7)	0.65
					placebo		21	132 (sd=15)	final=131 (sd=16)		.
				Secondary-Diastolic Blood Pressure	D 7000 IU cholecalciferol		22	85 (sd=10)	final=84 (sd=11)	0 (-7, 7)	1
					placebo		21	81 (sd=10)	final=84 (sd=11)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Wamberg et al., 2013	RCT/CCT	Y	ND	Y	Y	Y	Y	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Wang et al., 2013	Prospective Cohort	19–50 years; 51–70 years; Healthy; Male physicians; 40–84 years of age	Prior cancer; Current cancer; Current cardiovascular disease; Hypertension; chronic disease	Physicians' Health Study (PHS)	Government	USA	660/660/0	57.6 (7.6)/40–84			Winter/spring: 55.9±22.5 Summer/fall: 77.4±26.2

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Wang et al., 2013	Prospective Cohort	Not relevant	Other Nutrients Or Dietary Factors- Multivitamin Use; Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Smoking, Other Lifestyle Factors- Smoking (Never, Past, Current), Alcohol Use, Vigorous Exercise; Other - History Of Hyperlipidemia	Primary- Hypertension	25(OH)D	Q1: 13.0–57.8	15.3 yrs	97/164	adjusted/HR	1	Reference	0.43
					25(OH)D	Q2: 37.0–74.9	15.3 yrs	97/164	adjusted/HR	0.94	0.69, 1.27	
					25(OH)D	Q3: 48.6–93.5	15.3 yrs	79/167	adjusted/HR	0.67	0.50, 0.96	
					25(OH)D	Q4: 68.8–167.2	15.3 yrs	94/165	adjusted/HR	0.82	0.60, 1.13	
					25(OH)D	<50	15.3 yrs	73/136	adjusted/HR	1	Reference	0.32
					25(OH)D	50–74	15.3 yrs	144/244	adjusted/HR	1.03	0.75, 1.42	
					25(OH)D	75–99	15.3 yrs	93/178	adjusted/HR	0.79	0.56, 1.11	
					25(OH)D	>=100	15.3 yrs	57/102	adjusted/HR	0.94	0.62, 1.40	
					1,25(OH)D	Q1: 29.9–79.3	15.3 yrs	87/162	adjusted/HR	1	Reference	0.16
					1,25(OH)D	Q2: 68.0–88.2	15.3 yrs	80/162	adjusted/HR	0.92	0.66, 1.27	
					1,25(OH)D	Q3: 80.8–101.8	15.3 yrs	95/165	adjusted/HR	1.12	0.82, 1.54	
					1,25(OH)D	Q4: 94.0–177.6	15.3 yrs	101/162	adjusted/HR	1.19	0.86, 1.63	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Wang et al., 2013	Y	Y	Y	Y						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	NA	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Ward et al., 2010	RCT/CCT	9–18 years; Healthy; postmenarchal girls; attended an inner-city, multiethnic, all-girls school in Manchester UK	Pregnant; evidence of liver, kidney, or other disorders that may cause nonnutritional vitamin D deficiency or abnormal bone development; clinical signs of vitamin D deficiency		Government	UK; Manchester	72/65/100	13.8 (0.7)/12–14			total serum 25OHD placebo: 17.9 ± 7.4 nmol/l vit D group: 18.1 ± 8.0 nmol/l

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Ward et al., 2010	RCT/CCT	NR	Anthropometrics- Follow-Up Height, Baseline And Follow-Up Weight	Secondary-Maximum Force	Vit D2 150,000 IU/ quarterly		33	2.80 (SD=0.23)	change= -0.08 (SD=0.22)	-0.04 (-0.12, 0.04)	0.32
					Placebo		32	2.71 (SD=0.32)	change= -0.04 (SD=0.04)		.
				Secondary-Eslinger Fitness Index	Vit D2 150,000 IU/ quarterly		33	89.44 (SD=14.41)	change= -4.31 (SD=9.32)	+0.17 (-3.8, 4.2)	0.93
					Placebo		32	85.41 (SD=15.57)	change= -4.48 (SD=6.68)		.
				Secondary-Efficiency	Vit D2 150,000 IU/ quarterly		33	87.76 (SD=13.00)	change= 2.72 (SD=8.57)	+1.10 (-0.91, 3.12)	0.1
					Placebo		32	84.36 (SD=14.31)	change= -0.56 (SD=7.42)		.
				Secondary-Velocity	Vit D2 150,000 IU/ quarterly		33	2.19 (SD=0.21)	change= 0.02 (SD=0.13)	+0.03 (-0.03, 0.09)	0.28
					Placebo		32	2.12 (SD=0.24)	change= -0.01 (SD=0.09)		.
				Secondary-Jump Height	Vit D2 150,000 IU/ quarterly		33	0.34 (SD=0.06)	change= 0.01 (SD=0.04)	+0.01 (-0.01, 0.03)	0.32
					Placebo		32	0.33 (SD=0.06)	change= 0.00 (SD=0.04)		.
				Secondary-Maximum Power Relative To Body Weight	Vit D2 150,000 IU/ quarterly		33	39.52 (SD=6.21)	change= -1.06 (SD=4.18)	+0.18 (-1.6, 2.0)	0.84
					Placebo		32	37.81 (SD=6.81)	change= -1.24 (SD=2.91)		.
				Secondary-Spine Bone Mineral Content (BMC)	Vit D2 150,000 IU/ quarterly		35	11.73 (SD= 1.99)	change= 0.52 (SD=0.39)	-0.05 (-0.24, 0.15)	0.62
					Placebo		33	11.97 (SD= 1.97)	change= 0.57 (SD=0.43)		.
				Secondary-Tibia 66% Cortical Bone Mineral Content (Ct BMC)	Vit D2 150,000 IU/ quarterly		33	268.38 (SD= 38.85)	change= 7.68 (SD=12.26)	-1.98 (-8.4, 4.4)	0.54
					Placebo		31	261.23 (SD= 38.06)	change= 9.66 (SD=13.38)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Ward et al., 2010	RCT/CCT	Y	Y	ND	Y	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Wei et al., 2012	Prospective Cohort	Pregnant or lactating women; between 12 and 18 completed weeks of pregnancy on the basis of last menstrual period and confirmed by early ultrasound examination	women who had a history of medical complications including endocrine disease (e.g., thyroid disease), renal disease with altered renal function, epilepsy, any collagen vascular disease (e.g., systemic lupus erythematosus and scleroderma), active and chronic l; regularly consumed supplements 200 mg/day for vitamin C and/or 50 IU/day for vitamin E; took warfarin; women who had known fetal abnormalities (e.g., hydatidiform mole), or known fetal chromosomal or major malformations in the current pregnancy; women with repeated spontaneous abortion (women with a previous bleeding in the first trimester were included if the site documented a viable fetus at the time of recruitment; women who used an illicit drug during the current pregnancy	International Trial of Antioxidants in the Prevention of Pre-eclampsia (INTAPP)	Government	Canada	697/697/100	30.3 (4.8)/NR	Non-Hispanic White=892; Not reported=118	Other; 31.3% in high-risk group including chronic hypertension, prepregnancy diabetes, multiple pregnancy, or a history of pre-eclampsia	NR

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Wei et al., 2012	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- Prepregnancy BMI; Medical Conditions- Risk Group (See Comments); Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking	Primary- Preeclampsia	25(OH)D	per SD increase	12–18 weeks gestation	32/697	adjusted/OR	0.79	0.52, 1.20	NR
					25(OH)D	<50	12–18 weeks gestation	15/272	adjusted/OR	1.24	0.58, 2.67	NR
					25(OH)D	>50	12–18 weeks gestation	17/425	adjusted/OR	1	Reference	NR
					25(OH)D	per SD increase	24–26 weeks gestation	28/604	adjusted/OR	0.68	0.44, 1.05	NR
					25(OH)D	<50	24–26 weeks gestation	19/236	adjusted/OR	3.24	1.37, 7.69	NR
					25(OH)D	>50	24–26 weeks gestation	9/368	adjusted/OR	1	Reference	NR

Quality of Cohort or Nested Case-Control Studies										
Author, Year	**Eligibility Criteria Clear?**	**Sampling of Population Random or Consecutive?**	**Exposure Assessor Blinded to Outcome?**	**Outcome Assessor Blinded to Exposure Measurement?**	**Method Reported?**	**Food Composition Database or Suppl Composition Reported?**	**Internal Calibration?**	**One of the Prespecified Biomarkers Methods Used?**	**Time From Sample Collection to Sample Analysis Reported?**	**Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)**
Wei et al., 2012	Y	Y	N	N				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Wei et al., 2013	Prospective Cohort	Pregnant or lactating women; 12–18 weeks gestation	Current cardiovascular disease; use of warfarin; use of vitamin C or vitamin E prior to main intervention; collagen vascular disease; carrying a fetus with a known abnormality; endocrine disease; renal disease; epilepsy; use of an illicit drug during pregnancy; active or chronic liver disease; repeated spontaneous abortion	INTAPP	Government	Canada	697/NR/100	28.68 (5.44)/NR	Non-Hispanic White=3400; Hispanic=3484 ; Non-Hispanic Black=134; Asian=135; Race_other1= 2337; Race_other2= 042		NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Wei et al., 2013	Prospective Cohort	not relevant	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- Prepregnancy BMI; Sun Exposure- Season Of Blood Draw; Smoking, Other Lifestyle Factors- Smoking; Other - Preeclampsia Risk Status	Primary- Preeclampsia	25(OH)D	<50 nmol/L	24–26 weeks gestation	NR/NR	adjusted/OR	2.97	1.23, 7.20	
					25(OH)D	>=50 nmol/L	24–26 weeks gestation	NR/NR	adjusted/OR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Wei et al., 2013	N	Y	Y	N						N

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Welsh et al., 2012	Prospective Cohort	19–50 years; 51–70 years; offspring of married couples in the Renfrew/Paisley cohort; aged 30–59 years; living locally	problematic addresses (addresses provided by parents or death certificate informants which, for reasons of completeness or accuracy, could not be located in a current postcode directory); died before study commenced	MIDSPAN Family Study	Private Foundation	UK; Renfrew and Paisley	2081/1492/54 %	45.2 (6.2)/NR	Non-Hispanic White=100	Vitamin d deficient/depleted; Other; vitamin D not deficient	serum 25OHD vitamin D not deficient group (=15 ng/ml): 22.9 ng/ml vitamin D deficient group (<15 ng/ml): 11.0 ng/ml

Main Analyses												
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Vitamin D/ Calcium Measure**	**Exposure/ Intervention**	**Follow-up**	**N Event/ N Total**	**Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)**	**Result**	**95% CI**	**P-val**
Welsh et al., 2012	Prospective Cohort	NR	Other Nutrients Or Dietary Factors- Percent Fat From Diet, High And Low Fiber In Diet, Vitamin D Intake, Adjusted Calcium; Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Highest Educational Level, Social Class, Deprivation Category; Anthropometrics- BMI, Waist Circumference; Medical Conditions- Diabetes, Baseline Coronary Heart Disease; Sun Exposure- Season; Smoking, Other Lifestyle Factors- Smoking, Alcohol Intake, Low Baseline Physical Activity; Other - Systolic Blood Pressure, HDL And Total Cholesterol, Current Medication (Ace Inhibitors, Antihypertensives, Aspirin, Insulin, Oral Hypoglycemic, Spartans, Statins)	Primary-All-Cause Mortality	25(OH)D	per 1 SD increase	14.4 yrs	70/1492	adjusted/HR	0.74	0.56, 0.99	
					25(OH)D	Deficient, <15 ng/ml	14.4 yrs	NR/689	adjusted/HR	2.02	1.17, 3.51	
					25(OH)D	Not deficient =15 ng/ml	14.4 yrs	NR/803	adjusted/HR	1	reference	
				Primary-Cardiovascular Event	Dietary Vit D intake	per 1 SD increase in dietary Vit D intake-log scale	14.4 yrs (median)	293/1492	Adjusted/HR	0.94	0.83, 1.08	NR
					25(OH)D	per 1 SD increase in 25(OH)D-log scale	14.4 yrs (median)	293/1492	Adjusted/HR	1.07	0.94, 1.23	NR
					25(OH)D	<15ng/ml	14.4 yrs (median)	293/1492	Adjusted/HR	1	0.77, 1.31	NR
					25(OH)D	>=15 ng/ml	14.4 yrs (median)		Adjusted/HR	1	Reference	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Welsh et al., 2012	Y	Y	N	N				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Witham et al., 2013	RCT/CCT	9–18 years; 19–50 years; 51–70 years; age 18 or over; serum 25(OH)D<75; female; South Asian origin	any except fish oil; symptomatic; estimated GFR<40; Liver function tests more than 3-fold upper limit of normal; adjusted serum calcium>2.60 or <2.15 mmol/L; History of renal calculi; sarcoidosis or metastatic malignancy; childbearing age and not using birth control		University	UK	50/50/100	39.4 (11.8)/NR	Race_other1= 100		<50 nmol/L

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Witham et al., 2013	RCT/CCT	Not relevant	Other Nutrients Or Dietary Factors- Baseline 25(Oh)d; Anthropometrics- BMI; Other - Flow Mediated Dilation, PTH, Total Cholesterol	Secondary-Systolic Blood Pressure	D3 100,000 units		25	119 (sd=15)	change=2.0 (sd=7.9)	+3.0 (-1.9, 8.0)	.
					D3 placebo		25	122 (sd=19)	change=-1.0 (sd=9.1)		.
				Secondary-Diastolic Blood Pressure	D3 100,000 units		25	78 (sd=11)	change=-0.1 (sd=5.7)	+0.6 (-2.5, 3.7)	.
					D3 placebo		25	78 (sd=13)	change=-0.7 (sd=5.2)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Witham et al., 2013	RCT/CCT	Y	Y	NA	Y	ND	N	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Wong et al., 2013	Prospective Cohort	51–70 years; 65 years and older	Not specified		Government	Australia;Perth	4203/4203/0	76/70–88		Not Reported	NR

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Wong et al., 2013	Prospective Cohort	NR	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Medical Conditions- Cardiovascular Disease, Diabetes, Hypertension, Dyslipidemia, Charlson's Comorbidity Index, Renal Function; Smoking, Other Lifestyle Factors- Smoking; Other - Season, Baseline Frailty Status	Primary-All-Cause Mortality	25(OH)D	per 10nmol/L decrease in 25(OH)D	6.7 yrs	1144/4203	adjusted/HR	1.04	1.01, 1.07	
					25(OH)D	halving of 25(OH)D	6.7 yrs		adjusted/HR	1.21	1.08, 1.35	
					25(OH)D	Q1: 10–52.8	6.7 yrs		adjusted/HR	1.2	1.02, 1.42	
					25(OH)D	Q2: 52.9–67.3	6.7 yrs		adjusted/HR	1	Reference	
					25(OH)D	Q3: 67.4–81.6	6.7 yrs		adjusted/HR	0.99	0.84, 1.17	
					25(OH)D	Q4: 81.7–238.4	6.7 yrs		adjusted/HR	0.99	0.83, 1.17	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Wong et al., 2013	Y	Y	N	N						Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	N	NA	Y	N	N	B	ref 18: http://ije.oxfordjournals.org/content/38/1/48.full.pdf+html

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Wood et al., 2012	RCT/CCT	Postmenopausal women; Caucasian	CVD; diabetes, asthma, malabsorption, hypertensive blood pressure measurements of at least 160 mm Hg systolic or 99 mm Hg diastolic; difficulty in swallowing tablets or capsules; medications or supplements known to affect any dependent variable; current smokers; abnormal blood biochemistry at screening		Government	UK; Aberdeen	305/197/100	63.9 (2.3)/NR	Non-Hispanic White=100	Post menopausal	Serum 25(OH)D placebo: 36.18 ± 17.1 nmol/l 400 IU D3 group: 32.74 ± 12.9 nmol/l 1000 IU D3 group: 32.41 ± 13.8 nmol/l

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Wood et al., 2012	RCT/CCT	NR	Other Nutrients Or Dietary Factors- Serum Calcium (Adjusted For Albumin), Serum Total 25(OH)d, Plasma PTH; Anthropometrics- Baseline Measurements Of Weight; Smoking, Other Lifestyle Factors- Physical Activity Level; Other - Grip Strength, Weekly Sed, Serum Calcium Concentrations, Baseline Adipose Tissue Distribution	Secondary-DBP	D3 400 IU Vit D/day		97	77.68 (sd=7.3)	change=-2.5 (-3.6, -1.4)	-0.4 (-1.9, 1.1)	.
					D3 placebo		100	77.7 (sd=7.8)	change=-2.1 (-3.1, -1.0)		.
				Secondary-SBP	D3 400 IU Vit D/day		96	128.16 (sd=13.8)	change=-2.2 (-3.3, -0.7)	+0.2 (-2.2, 2.6)	.
					D3 placebo		98	128.18 (sd=13.3)	change=-2.4 (-4.5, -0.2)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Wood et al., 2012	RCT/CCT	Y	ND	Y	N	Y	Y	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Woodham et al., 2011	Nested Case Control	Pregnant or lactating women; previously given blood for routine genetic multiple marker screening and subsequently delivered at the University of North Carolina-Chapel Hill between Jan 2004 and Nov 2008	kidney disease, diabetes mellitus, known thrombophilias, any other significant preexisting chronic medical disease; multiple gestation; major congenital fetal anomalies; pregestational hypertension		Government	UK; Chapel Hill	164/164/100	median: 29/IQR: 25–33	Non-Hispanic White=29; Hispanic=27; Non-Hispanic Black=39; Asian=5	Not Reported	Serum 25(OH)D - median (IQR) controls: 107 (90–121) nmol/l cases: 75 (53–107) nmol/l

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Woodham et al., 2011	Nested Case Control	race/ethnicity	Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- BMI; Sun Exposure- Season Of Blood Draw; Other - Gestational Age At Blood Draw, Sflt-1/Plgf Ratio [soluble Fms-Like Tyrosine Kinase-1, Placental Growth Factor]	Primary-Severe Preeclampsia	25(OH)D	NR	NR	41/164	adjusted/OR	0.95	0.94, 0.97	

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Woodham et al., 2011	Y	Y	N	N				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Woolcott et al., 2010	Nested Case Control	51–70 years; age 45–75 years	Not specified	Multiethnic Cohort	Government	USA; Hawaii, Los Angeles	633/663/35.9 (controls)	69.2 (7.9)/NR	Non-Hispanic White=171; Non-Hispanic Black=187; Race_other1=394; Race_other2=88; Race_other3=46	Not Reported	Plasma 25(OH)D controls: 25.0 ± 9.9 ng/ml cases: 23.2 ± 10.1 ng/ml

Main Analyses												
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Vitamin D/ Calcium Measure	Exposure/ Intervention	Follow-up	N Event/ N Total	Crude or Adjusted/ Outcome Metric (e.g. OR,RR,HR,%)	Result	95% CI	P-val
Woolcott et al., 2010	Nested Case Control	sex, race/ethnicity, study area, data (±6 mo) and time (±2 h) between blood draw and case diagnosis, birth year (±1 y), hours fasting before blood draw (8 to <10 h, =10 h)	Demographics (Age, Sex, Race/Ethnicity)- Age, Sex, Race/Ethnicity; Anthropometrics- BMI; Other - Data And Time Of Blood Draw, Hours Fasting, Family History Of Colon Cancer, Intake Of Processed Red Meat	Primary-Colorectal Cancer	25(0H)D	<16.8ng/mL	NR	67/154	adjusted/OR	1	reference	
					25(0H)D	16.8<22.2ng/mL	NR	42/128	adjusted/OR	0.63	0.37, 1.08	
					25(0H)D	22.2<26.3ng/mL	NR	38/126	adjusted/OR	0.54	0.32, 0.93	
					25(0H)D	26.3<32.8ng/mL	NR	43/130	adjusted/OR	0.62	0.36, 1.07	
					25(0H)D	>=32.8ng/mL	NR	39/125	adjusted/OR	0.6	0.33, 1.07	
					25(0H)D	Per doubling	NR	NR/663	adjusted/OR	0.68	0.51, 0.92	0.010

Quality of Cohort or Nested Case-Control Studies										
Author, Year	Eligibility Criteria Clear?	Sampling of Population Random or Consecutive?	Exposure Assessor Blinded to Outcome?	Outcome Assessor Blinded to Exposure Measurement?	Method Reported?	Food Composition Database or Suppl Composition Reported?	Internal Calibration?	One of the Prespecified Biomarkers Methods Used?	Time From Sample Collection to Sample Analysis Reported?	Level of Exposure in Comparative Categories Given? (Categorical Analyses Only)
Woolcott et al., 2010	Y	Y	Y	Y				Y	N	Y

Quality of Cohort or Nested Case-Control Studies									
Adjusted or Matched for Any Confounders? (Besides Age and Sex)	Justification of Final Adjusted Model Selection?	Clear Definition of Outcome Including Time of Ascertainment?	Loss to Followup <20%?	Do the Authors Specify a Primary Outcome?	Prospective Collection of Data?	Analysis Was Planned When Cohort Was Formed?	Justification of Sample Size (Includes Sample Size Calculations)?	Overall Grade	Explanation for Grade (if Not A)
Y	Y	Y	Y	Y	Y	N	N	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	Study Design	Inclusion	Exclusion	Trial or Cohort Name	Funding	Location	N Enrolled/ N Analyzed/ Percent Female	Age Mean(SD)/ Age Range	Race/ Ethnicity	Health Status	Specific Nutrition Status
Zhu et al., 2008	RCT/CCT	9–18 years; age 10 years; girls	Not specified		Manufacturer	China; Beijing	757/235/100	10.1 (0.3)/NR			Vit D intake Control group – 0.9 ± 0.6µg/d CaD milk – 0.9 ± 0.6µg/d

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Zhu et al., 2008	RCT/CCT	NR	Other Nutrients Or Dietary Factors- Ca Intake, Vitamin D Intake; Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- Height, Weight; Other - Tanner Breast Stage, Tanner Pubic Hair Stage, Post-Menarche	Secondary-Midriff BMD size-corrected (sc)	D3 560 mg calcium + 5–8 µg Vit D/school day		112	1585 (sd=332)	final=1803 (sd=446)	+43 (-79, 165)	.
					D3 control (no supplementary milk and habitual diet)		123	1584 (sd=337)	final=1760 (sd=499)		.
				Secondary-Pelvis BMD sc	D3 560 mg calcium + 5–8 µg Vit D/school day		112	46 (sd=4)	final=49 (sd=7)	0 (-1.9, 1.9)	.
					D3 control (no supplementary milk and habitual diet)		123	47 (sd=5)	final=49 (sd=8)		.
				Secondary-Total Body BMD sc	D3 560 mg calcium + 5–8 µg Vit D/school day		112	93 (sd=5)	final=95 (sd=10)	+3 (0.3, 5.7)	.
					D3 control (no supplementary milk and habitual diet)		123	95 (sd=6)	final=92 (sd=11)		.

Quality of Interventional Studies												
Author, Year	Study Design	Appropriate Randomization Technique (Y/N/ND/NA)	Allocation Concealment (Y/N/ND/NA)	Appropriate Washout Period (Y/N/ND/NA)	Dropout Rate <20%	Blinded Outcome Assessment (Y/N/ND)	Intention to Treat Analysis (Y/N/ND)	Appropriate Statistical Analysis (Y/N)	Assessment for Confounding (Y/N/ND/NA)	Clear Reporting w/o Discrepancies (Y/N)	Overall Grade	Explanation for Grade (if Not A)
Zhu et al., 2008	RCT/CCT	ND	ND	ND	Y	Y	ND	Y	ND	Y	B	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Zhu et al., 2010	RCT/CCT	51–70 years; age 70–90 years; plasma 25(OH)D concentration less than 24 ng/ml; history of at least one fall in the previous 12 months	current consumption of vitamin D or bone or mineral active agents apart from calcium; BMD Z-score at total hip site of less than -2.0; medical conditions or disorders that influence bone mineral metabolism; fracture in the past 6 months; Mini-Mental State Examination score less than 24 or the presence of significant neurological conditions likely to substantially impair balance or physical activity such as stroke; Parkinson's disease		Manufacturer	Australia;Perth	302/261/100	77.0 (4.8)/NR	Non-Hispanic White=970; Asian=30; Race_other1=0	Other; plasma 25(OH)D concentration less than 24 ng/mL	Serum 25(OH)D 17.7 ± 4.2 ng/ml

Main Analyses											
Author, Year	Study Design	Characteristics Matched on	Controlled Confounders	Primary or Secondary Outcome	Exposure Intervention	Follow-up	N Analyzed	Baseline Mean/ (CI/SE/SD)	Final or Delta/ (CI/SE/SD)	Net Difference/ (CI/SE/SD)	P-between Groups
Zhu et al., 2010	RCT/CCT	NR	NR	Secondary-Timed Up And Go (TUAG)	Vit D2 + Calcium 1,000 mg/d calk +1,00 IU vit D2		129	11.0 (SD=5.3)	Final=8.1 (SD=3.9)	-0.9 (-2.2, 0.5)	0.2
					Placebo + Calcium 1,000 mg/d calk		132	10.8 (SD=4.6)	Final=9 (SD=7)		.
				Secondary-Lower Limb Muscle Strength: Ankle Dorsiflexion	Vit D2 + Calcium 1,000 mg/d calk +1,00 IU vit D2		129	11.6 (SD=4.4)	Final=10.9 (SD=3.7)	0 (-0.9, 0.9)	1
					Placebo + Calcium 1,000 mg/d calk		132	11.8 (SD=4.2)	Final=10.9 (SD=4)		.
				Secondary-Lower Limb Muscle Strength: Knee Flexor	Vit D2 + Calcium 1,000 mg/d calcium +1,00 IU vit D2		129	11.8 (SD=3.6)	Final=12.9 (SD=3.5)	-0.1 (-1.0, 0.8)	0.83
					Placebo + Calcium 1,000 mg/d calcium		132	11.9 (SD=3.7)	Final=13 (SD=3.9)		.
				Secondary-Lower Limb Muscle Strength: Knee Extensor	Vit D2 + Calcium 1,000 mg/d calcium +1,00 IU vit D2		129	18.3 (SD=6.4)	Final=18 (SD=5)	-0.3 (-1.6, 1.0)	0.65
					Placebo + Calcium 1,000 mg/d calcium		132	18.8 (SD=7.3)	Final=18.3 (SD=5.5)		.
				Secondary-Lower Limb Muscle Strength: Hip Extensor	Vit D2 + Calcium 1,000 mg/d calcium +1,00 IU vit D2		129	14.6 (SD=5.7)	Final=17.2 (SD=5.2)	+0.3 (-1.1, 1.7)	0.67
					Placebo + Calcium 1,000 mg/d calcium		132	14.4 (SD=5.3)	Final=16.9 (SD=6.2)		.
				Secondary-Lower Limb Muscle Strength: Hip Abductor	Vit D2 + Calcium 1,000 mg/d calcium +1,00 IU vit D2		129	12.3 (SD=4.2)	Final=14.5 (SD=4.1)	+0.4 (-0.7, 1.5)	0.48
					Placebo + Calcium 1,000 mg/d calcium		132	12.2 (SD=5)	Final=14.1 (SD=4.9)		.
				Secondary-Lower Limb Muscle Strength: Hip Flexor	Vit D2 + Calcium 1,000 mg/d calcium +1,00 IU vit D2		129	14.5 (SD=5)	Final=15.4 (SD=4.2)	0 (-1.1, 1.1)	1
					Placebo + Calcium 1,000 mg/d calcium		132	14.5 (SD=5.7)	Final=15.4 (SD=4.8)		.

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
				Secondary-Lower Limb Muscle Strength: Hip Adductor	Vit D2 + Calcium 1,000 mg/d calcium +1,00 IU vit D2		129	14.4 (SD=4.7)	Final=16.4 (SD=4.2)	+0.1 (-1.1, 1.3)	0.86
					Placebo + Calcium 1,000 mg/d calcium		132	14.7 (SD=5)	Final=16.3 (SD=5.2)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Zhu et al., 2010	RCT/CCT	Y	ND	Y	Y	Y	N	Y	Y	Y	A	

Eligibility Criteria and Baseline Characteristics											
Author, Year	**Study Design**	**Inclusion**	**Exclusion**	**Trial or Cohort Name**	**Funding**	**Location**	**N Enrolled/ N Analyzed/ Percent Female**	**Age Mean(SD)/ Age Range**	**Race/ Ethnicity**	**Health Status**	**Specific Nutrition Status**
Zhu et al., 2013	RCT/CCT	19–50 years; Healthy; absence of coronary heart disease, hypertension, diabetes, dyslipidemia; BMI =24 kg/m2 or more or BMI of 28; age 18–25 years; daily calcium intake <600 mg	Pregnant; use of calcium supplements or any medication that could affect body weight within 30 days of screening, no smoking; participating in any weight loss programs or in any other clinical trial; lactation		Government	China; Shanghai	53/43/85.7%	20.3 (0.8)/NR			Habitual Ca intake CaD group - 426.5 +/- 152.2 mg/d Control group - 392.1 +/- 141.1 mg/d

Main Analyses											
Author, Year	**Study Design**	**Characteristics Matched on**	**Controlled Confounders**	**Primary or Secondary Outcome**	**Exposure Intervention**	**Follow-up**	**N Analyzed**	**Baseline Mean/ (CI/SE/SD)**	**Final or Delta/ (CI/SE/SD)**	**Net Difference/ (CI/SE/SD)**	**P-between Groups**
Zhu et al., 2013	RCT/CCT	NR	Other Nutrients Or Dietary Factors- Initial Calcium Intake; Demographics (Age, Sex, Race/Ethnicity)- Age; Anthropometrics- Baseline Body Weight	Secondary-DBP	D3 (energy-restricted diet+600 mg calcium+125 IU Vit D)/day		22	70.7 (sd=7.1)	final=64.2 (sd=4.7)	-1.2 (-4.6, 2.2)	.
					D3 energy-restricted diet alone (control)		21	70 (sd=7.8)	final=65.4 (sd=6.3)		.
				Secondary-SBP	D3 (energy-restricted diet+600 mg calcium+125 IU Vit D)/day		22	119.2 (sd=10.5)	final=109.6 (sd=9.9)	-2.3 (-8.6, 4.0)	.
					D3 energy-restricted diet alone (control)		21	123 (sd=10.5)	final=111.9 (sd=10.4)		.

Quality of Interventional Studies												
Author, Year	**Study Design**	**Appropriate Randomization Technique (Y/N/ND/NA)**	**Allocation Concealment (Y/N/ND/NA)**	**Appropriate Washout Period (Y/N/ND/NA)**	**Dropout Rate <20%**	**Blinded Outcome Assessment (Y/N/ND)**	**Intention to Treat Analysis (Y/N/ND)**	**Appropriate Statistical Analysis (Y/N)**	**Assessment for Confounding (Y/N/ND/NA)**	**Clear Reporting w/o Discrepancies (Y/N)**	**Overall Grade**	**Explanation for Grade (if Not A)**
Zhu et al., 2013	RCT/CCT	Y	N	ND	Y	N	Y	Y	N	Y	B	

Appendix D. Evaluation of Existing Systematic Reviews and Evidence Tables of the Qualified Systematic Reviews

List of Acronyms and Abbreviations

Acronym/Abbreviation	Term
BP	Blood pressure
Ca	Calcium
CRC	Colorectal cancer
DBP	Diastolic blood pressure
HTN	Hypertension
im	intramuscular
NTN	Normotensive
OR	Odds ratio
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SE	Standard error

Evaluation of existing systematic reviews

Author Year Journal/Source	Intervention or Exposure	Outcome	Study Design Included	Healthy Population at Baseline?*	Only Included Ca +- Vit D Interventions?† Reported Baseline Dietary Ca Intake With Dietary Assessment Methods?‡	Clear Reporting of Comparison and Control Group?	Clear Reporting of Outcome Definitions?	Clear Reporting of Study Designs (Need Separate Reporting if Two or More Different Designs Are Included)?	Comments§
Included in Current Report									
Wang, 2012 Circulation Cardiovascular Quality and Outcomes [23149428]	Vitamin D (serum 25(OH)D)	Cardiovascular disease risk	Prospective	Yes and no	Not relevant	Yes	Yes	Yes	Many studies included in current or original report
Autier, 2012 J Clin Endocrinol Metab [22701014]	Vitamin D [+/- Calcium]	Serum 25(OH)D concentration	RCTs	Yes	Yes	Yes	Yes	Yes	Included a small number of studies of im administration
Included in Original Report									
Autier 2007 Arch Intern Med [17846391]**	Vitamin D [+/- Calcium]	All cause mortality	RCTs	Yes	Yes	Yes	Yes	Yes	One additional study found
Avenell 2008 Cochrane Database of Systematic Reviews [16034849]§§	Vitamin D [+/- Calcium]	All cause mortality	RCTs	Yes	Yes	Yes	Yes	Yes	All relevant studies included in Autier 2007– Conclusions are same as Autier 2007.
Allender 1996 Ann Intern Med	Ca supplement	Blood pressure	RCT	Yes (subgroup analysis)	Yes	Yes	Yes	Yes	26 of 64 potential RCTs
Cappuccio 1995 AJE	Ca intake	Blood pressure	Observ-ational, including cross-sectional	Unclear	No	NA (regressions)	Yes	No	REJECT Includes XS

Author Year Journal/Source	Intervention or Exposure	Outcome	Study Design Included	Healthy Population at Baseline?*	Only Included Ca +- Vit D Interventions?† Reported Baseline Dietary Ca Intake With Dietary Assessment Methods?‡	Clear Reporting of Comparison and Control Group?	Clear Reporting of Outcome Definitions?	Clear Reporting of Study Designs (Need Separate Reporting if Two or More Different Designs Are Included)?	Comments§
Dickinson 2008 Cochrane	Ca supplement	Blood pressure	RCT	No All with HTN	Yes	Yes	Yes	Yes	Revision of 2006 SR 15/64 potential RCTs
Griffith 1999 AJH	Ca supplement	Blood pressure	RCT	Yes & No HTN & NTN combined See comment	Yes	Yes	Yes	Yes	Update of Bucher 1996 [2263] Subgp analysis HTN vs NTN in Bucher only 42/64 potential RCTs
van Mierlo 2006 J Hum Hypert	Ca supplement	Blood pressure	RCT	Yes Subgroup of HTN & NTN	Yes	Yes	Yes	Yes	40/64 potential RCTs
Trumbo 2007 Nutr Rev	Ca supplement	Blood pressure, HTN, Pregnancy-induced HTN	All	Yes Subgroup of HTN & NTN	Yes (interv) No (observ)	No	No	No	REJECT Qualitative only Count of sig studies only Unclear if SR.
Bergsma-Kadijk 1996 Epidemiology	Ca intake	cancer and polyp	Cohort and Case-control	nd (probably healthy population)	nd on dietary assessment method	nd on Ca intake (only RR/OR between lowest and highest categories reported)	nd	nd on the definition of case-control study	Reject
Weigarten 2008 Cochrane Database of Systematic Reviews	Ca supplement (>1200 mg/d)	cancer and polyp	RCT	yes (pts with prior adenoma)	yes	yes	yes	yes	Accept

Author Year Journal/Source	Intervention or Exposure	Outcome	Study Design Included	Healthy Population at Baseline?*	Only Included Ca +- Vit D Interventions?† Reported Baseline Dietary Ca Intake With Dietary Assessment Methods?‡	Clear Reporting of Comparison and Control Group?	Clear Reporting of Outcome Definitions?	Clear Reporting of Study Designs (Need Separate Reporting if Two or More Different Designs Are Included)?	Comments[§]
Davies 2006 J Natl Cancer Inst	Nutritional RCTs, including Ca supplement	Cancer, recurrence of preinvasive lesions	RCT	No (both pts with cancer and preinvasive lesions)	nd	no	no	yes	Part of a larger SR of both diet and physical activity on outcome among patients with cancer or preinvasive lesions
Bergel 2007 BMC Pediatrics	maternal calcium intake	offspring BP	RCTs & cohort	y (RCT)	no yes	yes	yes	no	Data from 2 RCTs may be useful. Reject
Carroli 1994 Brit J Obstet Gynecol	Ca supplement	Preeclampsia	RCT	Yes	Yes	Yes	Yes	Yes	Covered by latest Cochrane SR
Hofmeyer 2003 S African J	Ca Supplement	Preeclampsia	RCT	Yes	Yes	Yes	Yes	Yes	Covered by latest Cochrane SR
Hofmeyer 2007 S African J	Ca Supplement	Preeclampsia (and summary of the outcomes mentioned above)	RCT	Yes	Yes	Yes	Yes	Yes	Covered by latest Cochrane SR

Author Year Journal/Source	Intervention or Exposure	Outcome	Study Design Included	Healthy Population at Baseline?*	Only Included Ca +- Vit D Interventions?† Reported Baseline Dietary Ca Intake With Dietary Assessment Methods?‡	Clear Reporting of Comparison and Control Group?	Clear Reporting of Outcome Definitions?	Clear Reporting of Study Designs (Need Separate Reporting if Two or More Different Designs Are Included)?	Comments[§]
Hoffmeyr 2006 Cochrane Database of Systematic Reviews	Ca supplement	Preeclampsia, pregnancy induced hypertension with and without proteinuria, maternal death or serious morbidity, other maternal outcomes, stillbirth, neonatal mortality or morbidity, preterm birth, small gestational age, and other outcomes for the child	RCT	Yes	Yes	Yes	Yes	Yes	Eligible review
Bucher 1996 JAMA	Ca supplement	Preeclampsia, pregnancy-induced hypertension	RCT	Yes	Yes	Yes	Yes	Yes	Covered by latest Cochrane SR
Gao 2005 NCI	calcium intake or dairy product	prostate cancer	prospective cohort	yes (assumed from study design)	yes	yes	yes	yes	
Shaukat 2005 Am J Gastroenterol	Ca supplement	recurrent polyp	RCT	yes (pts with prior adenoma)	no (1/3 included Ca+Vit A/C/E+selenium)	yes	yes? “recurrence of adenoma”	yes? “RCT”	Reject

Author Year Journal/Source	Intervention or Exposure	Outcome	Study Design Included	Healthy Population at Baseline?*	Only Included Ca +- Vit D Interventions?† Reported Baseline Dietary Ca Intake With Dietary Assessment Methods?‡	Clear Reporting of Comparison and Control Group?	Clear Reporting of Outcome Definitions?	Clear Reporting of Study Designs (Need Separate Reporting if Two or More Different Designs Are Included)?	Comments§
Barr 2003 J Nutr	Increased dairy product or calcium intake (from supplements)	Weight	RCTs	Yes "healthy"	Yes (separate studies of increased dairy product and those of calcium supplements)	yes	yes	yes	No meta-analysis. Included children and adults
Trowman 2006 Br J Nutr	Calcium supplements or increased provision of dairy products	Weight	RCTs	Yes (excluded populations with severe co-morbidities, such as renal problems or cancer)	Yes (Separate meta-analyses for calcium supplement and increased provision of dairy products)	yes	yes	yes	May need to redo the meta-analyses to separate out energy restriction diet studies. This SR included adults only.
Winzenberg 2007 Obesity	calcium supplementa-tion food or chemical	weight	RCTs	yes	yes	yes	yes	yes	2º analysis of RCT of calcium on bone density outcome
Lanou 2008 Nutr Rev	Calcium or dairy supplementa-tion with or without energy restriction	Weight, body fat	RCTs	nd	yes	no	yes	yes	Included both dairy and calcium supplementati on RCTs. No individual study characteristics reported

*Either included only healthy population at baseline or SR had separate analyses for population with diseases and without diseases
†For SR of interventional studies
‡For SR of observational studies
§Please comment on issues such as update of previous SRs or specific reasons for using or not using the SR, other than not fulfilling the screening criteria.
**We excluded a study on patients with congestive heart failure in our reanalysis of data from this systematic review
§§Examined only trials on falls prevention

Evidence table of systematic review of Vitamin D supplementation on serum 25(OH)D concentrations

Author Year [PMID]	Autier 2012 [22701014]
Design	Systematic review of RCTs
Population	• Include adults 50 years and over • Exclude individuals with chronic diseases • Exclude trials of mainly non-Caucasian participants
Intervention (Exposure) and Comparator	Intervention (Exposure): • Include vitamin D_2 or D_3 with or without calcium • Exclude other vitamin D compounds/analogs • Include oral and im supplementation • Exclude trials of fortified foods Comparator: • Placebo or no intervention (I.e., open-label included)
Results	See text for further summary of results: • Compared to D3, D2 was associated with lower increases in serum 25(OH)D concentration • Concomitant use of calcium and high baseline serum 25(OH)D were associated with smaller increases in serum 25(OH)D concentration
Comments	

AMSTAR			
A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	NR
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	Yes
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes		

Evidence table of systematic review of circulating 25(OH)D and Risk for Cardiovascular Disease

Author Year [PMID]	Wang 2012 [23149428]
Design	Systematic review of prospective studies and nested case control studies
Population	• Exclude studies of individuals with confirmed health conditions
Intervention (Exposure) and Comparator	Intervention (Exposure): • Include only studies that assessed serum 25(OH)D concentrations Comparator: • Individuals with different serum concentrations of 25(OH)D
Results	See text for further summary of results: • Baseline circulating 25(OH)D was associated with decreased risk for cardiovascular disease in many but not all studies
Comments	

AMSTAR			
A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	Yes
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	Yes
Included and excluded studies listed?	Yes/No	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes		

Evidence table of systematic review of the effect of vitamin D on bone health

Author Year [PMID]	Cranney 2007 [18088161]
Design	Systematic review of RCTs and observational studies
Population	• Include all ages • Exclude secondary causes of osteoporosis (e.g., glucocorticoid-induced, renal or liver disease) • Exclude studies on the treatment of vitamin D-dependent rickets (to minimize clinical heterogeneity as treatments is often non-dietary sources of vitamin D)
Intervention (Exposure) and Comparator	Intervention (Exposure): • Include vitamin D_2 or D_3 with or without calcium. • Exclude vitamin D preparations, calcitriol, alphacalcidol (because they are not nutritional supplements, and have different safety profile) Comparator: • No vitamin D or lower doses/levels of vitamin D
Results	See text for summary results for the following outcomes in both vitamin D and combined vitamin D and calcium sections of the report: • Rickets • Fractures, falls, or performance measures • Bone mineral density or bone mineral contents • How does dietary intake of vitamin D from fortified foods and vitamin D supplementation affect serum 25(OH)D Concentrations • Adverse events
Comments	Case-control studies were included but always summarized separately from cohort studies and RCTs. Meta-analyses were performed to pool results from RCTs only.

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	Yes
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	No	**Publication bias assessed?**	No
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes		

Evidence table of systematic review on vitamin D supplementation and all-cause mortality

Author Year [PMID]	Autier 2007 [17846391]
Design (Search Years)	Randomized controlled trials (1992-2006)
Population	Community dwelling or institutionalized adults
Intervention (Exposure) and Comparator	Supplementary vitamin D (at least 1000 mg/d) without calcium vs. placebo or no treatment
Results	18 trials of combined vitamin D and vitamin D + calcium RR: 0.93 (95% CI 0.87, 0.99); favoring vitamin D (± calcium) supplementation Statistically homogeneous In our reanalysis we and excluded 3 of 18 trials and separated studies with vitamin D only from those with vitamin D and calcium combination. For details and results of our reanalysis, see text.
Comments	See text in vitamin D and vitamin D + calcium sections for reanalyses of the separated trials. Study participants, vitamin D assays, and vitamin D status are not described in detail.

AMSTAR Criteria

A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	No	**Study quality appropriately used in analysis?**	NA
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	No	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes	The meta-analysis did not perform quality assessment (neither using individual quality items nor using quality scores)	

Evidence table of systematic review of calcium on growth in children

Author Year [PMID]	Winzenberg 2007 [17636098]
Design (Search Years)	Randomized controlled trials (1966-2005)
Population	Children <18 y
Intervention (Exposure) and Comparator	Supplemental and dietary calcium 300-1200 mg/d vs. placebo
Results	17 trials (2088 participants) Weighted mean difference: +0.14 (95% CI -0.28, +0.57) Kg; favors control Weighted mean difference: +0.22 (95% CI -0.30, +0.74) cm; favors control No significant statistical heterogeneity
Comments	Post hoc analysis performed on trials identified for a metaanalysis of randomized controlled trials of calcium on bone outcomes

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	No	**Publication bias assessed?**	Yes
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Unclear if all languages included; study quality assessed but not factored into the M-A	

Evidence table of systematic reviews of calcium and blood pressure

Author Year [PMID]	Griffith 1999 [10075392]
Design (Search Years)	Randomized controlled trials (1966-1997)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 600-2000 mg (36% 1000 mg; 26% 1500-1600 mg; 12% 2000 mg)
Results	42 trials SBP: -1.44 (-2.20, -0.68)*; statistically heterogeneous DBP: -0.84 (-1.44, -0.24); statistically heterogeneous Subgroup analyses did not find that heterogeneity could be explained by age, sex, baseline calcium, dietary versus nondietary calcium, or quality. Subgroups with hypertensive versus normotensive people were significantly different (no further details). Conclusions similar to previous systematic review (Bucher 1996{2263 /id})
Comments	Update of Bucher 1996{2263 /id} (see below).

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Study quality not discussed in conclusions. Funding source reported, but not conflict of interest.	

Author Year [PMID]	van Mierlo 2006 [16673011]
Design (Search Years)	Randomized controlled trials (1966-2003)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Calcium supplementation versus placebo (no supplement) Dose range 355-2000 mg (40% 1000 mg; 32% 1500-1600 mg; 6% 2000 mg)
Results	40 trials SBP: -1.86 (95% CI -2.91, -0.81); statistically heterogeneous DBP: -0.99 (95% CI -1.61, -0.37); statistically heterogeneous In multivariable analysis including age, sex, initial calcium intake, calcium dose, and initial blood pressure:

		SBP	DBP
Age	<45 y	-1.45 (-2.99, +0.09)	-1.26 (-2.20, -0.33)
	≥45 y	-2.33 (-3.69, -0.96)	-0.80 (-1.62, +0.02)
Male	≤50%	-2.20 (-3.68, -0.72)	-1.12 (-1.98, -0.26)
	>50%	-1.77 (-3.13, -0.42)	-0.84 (-1.65, -0.04)
Initial BP	<140/90 mm Hg	-2.04 (-3.40, -0.68)	-1.04 (-1.86, -0.22)
	≥140/90 mm Hg	-1.85 (-3.45, -0.32)	-0.89 (-1.79, +0.01)
Ca dose	≤1000 mg	-2.17 (-3.59, -0.75)	-1.41 (-2.24, -0.59)
	>1000 mg	-1.75 (-3.20, -0.31)	-0.56 (-1.40, +0.29)

Blood pressures not statistically significantly different between any strata.

Comments	

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Unclear	**Publication bias assessed?**	Yes
Included and excluded studies listed?	Partial	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes	No data on inclusion of unpublished data. Excluded studies available from authors	

Evidence table of systematic review s of calcium and blood pressure (continued)

Author Year [PMID]	Bucher 1996 [8596234]
Design (Search Years)	Randomized controlled trials (1966-1994)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 406-2000 mg (41% 1000 mg; 31% 1500-1600 mg; 8% 2000 mg)
Results	33 trials [Overall summary results were updated in Griffith 1999{1927 /id}, above] Studies with specified subgroups of hypertensive and normotensive participants (6 trials): Hypertensives SBP -4.30 (-6.47, -2.13) DBP -1.50 (-2.77, -0.23) Normotensives SBP -0.27 (-1.80, +1.27) DBP -0.33 (-1.56, +0.90) Regression analyses: BP (continuous scale) SBP OR = 0.99 (0.96, 1.01) DBP OR = 0.99 (0.96, 1.03) Dose of calcium, duration of supplementation, dietary vs nondietary calcium supplementation, methodological quality did not demonstrate a relationship with the magnitude of treatment effect.
Comments	Updated in Griffith 1999{1927 /id} (see above)

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	Yes
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Funding source reported, but not conflict of interest.	

Author Year [PMID]	Allender 1996 [8610952]
Design (Search Years)	Randomized controlled trials (1982-1993)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 400-2160 mg (35% 1000 mg; 29% 1500-1600 mg; 10% 2000 mg)
Results	26 trials (22 trials included in metaanalyses) SBP: -0.89 (-1.74, -0.05) DBP: -0.18 (-0.75, +0.40) Hypertensives SBP -1.68 (-3.18, -0.18) DBP +0.02 (-0.96, +1.00) Normotensives SBP -0.53 (-1.56, +0.49) DBP -0.28 (-0.99, +0.42) By weighted linear regression analyses, age, sex, calcium dose, trial duration were not associated with treatment effect (P>0.10)
Comments	

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	No
All publication types and languages included?	Yes	**Publication bias assessed?**	No
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Excluded studies not enumerated or listed. Fixed effects models used.	

Author Year [PMID]	Cappuccio 1989 [2697729]
Design (Search Years)	Randomized controlled trials (1983-1988)
Population	Both hypertensive and normotensive participants
Intervention and Comparator	Nondietary calcium supplementation versus placebo (no supplement) or low calcium intake Dose range 800-1600 mg (60% 1000 mg; 27% 1500-1600 mg)
Results	15 trials SBP (supine): -0.13 (-0.46, +0.19) DBP (supine): +0.03 (-0.17, +0.22) Hypertensives SBP +0.06 (-0.59, +0.72) DBP +0.03 (-0.21, +0.27)
Comments	

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	No
Two independent reviewers?	nd	**Study quality appropriately used in analysis?**	NA
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	No
All publication types and languages included?	nd	**Publication bias assessed?**	No
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Excluded studies not enumerated or listed. Fixed effects models used.	

Evidence table of systematic review s of calcium and blood pressure (continued)

Author Year [PMID]	Dickinson 2006 [16625609][†]
Design (Search Years)	Randomized controlled trials (1982-2003/2005[‡])
Population	Hypertensive participants
Intervention and Comparator	Dietary and nondietary calcium supplementation versus placebo (no supplement) Dose range 400-2000 mg (50% 1000 mg; 25% 1500-1600 mg; 6% 2000 mg)
Results	13 trials SBP: -2.53 (-4.45, -0.60); statistically heterogeneous DBP: -0.81 (-2.07, +0.44); statistically heterogeneous Ca dose <1200 mg SBP -2.67 (-5.15, -0.18) DBP -0.75 (-2.13, +0.63) Ca dose 1200-2000 mg SBP -2.69 (-5.86, +0.47) DBP -0.78 (-3.82, +2.25) Not statistically significantly different by calcium dose
Comments	

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	Yes
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	Yes	**Publication bias assessed?**	Yes
Included and excluded studies listed?	Yes	**Conflicts of interest stated?**	Yes
Study characteristics provided?	Yes		

[†]A technical update, with no further studies added was published in the Cochrane database in 2008.
[‡]Different dates for different databases.

Evidence table of systematic review of calcium on growth in children

Author Year [PMID]	Winzenberg 2007 [17636098]
Design (Search Years)	Randomized controlled trials (1966-2005)
Population	Children <18 y
Intervention (Exposure) and Comparator	Supplemental and dietary calcium 300-1200 mg/d vs. placebo
Results	17 trials (2088 participants) Weighted mean difference: +0.14 (95% CI -0.28, +0.57) Kg; favors control Weighted mean difference: +0.22 (95% CI -0.30, +0.74) cm; favors control No significant statistical heterogeneity
Comments	Post hoc analysis performed on trials identified for a metaanalysis of randomized controlled trials of calcium on bone outcomes

AMSTAR

A priori design?	Yes	**Study quality assessment performed?**	Yes
Two independent reviewers?	Yes	**Study quality appropriately used in analysis?**	No
Comprehensive literature search?	Yes	**Appropriate statistical synthesis?**	Yes
All publication types and languages included?	No	**Publication bias assessed?**	Yes
Included and excluded studies listed?	No	**Conflicts of interest stated?**	No
Study characteristics provided?	Yes	Unclear if all languages included; study quality assessed but not factored into the M-A	

Evidence table of systematic review on calcium intake and adenoma recurrence

Author Year [UI]	Weingarten, 2008 [18254022]
Design	Randomized controlled trials: Cochrane Library Issue 2, 2007, the Cochrane Colorectal Cancer Group (CCCG) specialized register, MEDLINE (1966 to July 2007), Cancerlit (1963 to April 2002), Embase (1980 to July 2007)
Population	Healthy adults and studies of adults at higher risk of colon cancer due to family history, previous adenomatous polyps, or inflammatory bowel disease
Intervention (Exposure) and Comparator	Calcium (>1200 mg/d) vs. placebo
Results	Calcium vs. placebo colorectal adenoma recurrence: OR 0.74, CI 0.58-0.95, P=0.02 CRC: OR 0.34, CI 0.05-2.15, P=0.20 at least one adverse event requiring discontinuation: OR 0.93, CI 0.42-2.05, P=0.80
Comments	Based only on two RCTs (1346 participants). Heterogeneity due to different dose of supplementation (one RCT supplemented with 1200 mg/d and the other RCT with 2000 mg/d). Analysis based on fixed effects model; however, considering there are only two studies, random effects model might have been more appropriate. Analysis on adverse events is based only on reported data of one out of the two RCTs (Barron 1999). Only participants with high risk due to previous adenomas were recruited in these two RCTs; therefore, applicability of the results can only be considered for high risk population. Insufficient evidence to recommend the general use of calcium supplements to prevent colorectal adenoma or colorectal cancer

AMSTAR

A priori design?	X	**Study quality assessment performed?**	X
Two independent reviewers?	X	**Study quality appropriately used in analysis?**	X
Comprehensive literature search?	X	**Appropriate statistical synthesis?**	X
All publication types and languages included?		**Publication bias assessed?**	
Included and excluded studies listed?	X	**Conflicts of interest stated?**	X
Study characteristics provided?	X		

Appendix E. Blank Data Extraction Form and Quality Assessment Checklists

Blank Data Extraction Form and Quality Assessment Checklists (From the Original Report)

ELIGIBILITY CRITERIA AND OTHER CHARACTERISTICS

UI	Author Year	Study Design*	Inclusion	Exclusion	Enrollment Years	Trial or Cohort Name	Funding Source	Extractor
		RCT RCT-post hoc** Other intervention study Cohort study Case-cohort study						

*Leave appropriate choice of study design and delete all others
**Post hoc analyses of an existing RCT for outcomes that were not planned in the original RCT

POPULATION (BASELINE)**

UI	Author Year	Study Design*	Location (e.g., City and Country, latitude)	N enrolled***	N analyzed	Mean (SD) Age, yr	Age Range / IQR	Male, %	Race / Ethnicity	Anthropometry Data (e.g., BMI, Weight, or %Body Fat …etc.)	Health Status	Specific Nutrition Status Data (e.g., Malnourish, Low Vit D or Ca Intake …etc.)

*Please copy from above
**Report baseline data for all subjects: preferred data for subjects actually analyzed than for subjects that enrolled in the study.
***For RCT, N enrolled is the number of subjects randomized. For cohort study, N enrolled is the total number of subjects fulfilled study inclusion criteria. For case-cohort study, please report as detailed information as possible on subjects selection. For example, original cohort sample size, number of subjects provided exposure data (e.g. blood sample or dietary assessment), number of subjects had outcome data …etc.

Background diet*

UI	Author Year	Exposure	Dietary Assessment Method**	Food Composition Database***	Internal Calibration (or Validity) of Dietary Assessment? (y/n) If Yes, Provide Data	Biomarker Assay****	Analytical Validity of Biomarker Data Reported? (y/n) If Yes, Provide Data	Time between Biomarker Sampling and Analysis	Season/Date when the biomarker samples were drawn	Background exposure data
		25(OH)D and/or 1,25$(OH)_2$D								
		Dietary calcium intake								

* Write "nd" if there was no data reported. Please do not leave blank
**Please refer to common dietary assessment method table. If other method was used, please describe the detail. Otherwise, please simply use the brief name described in the table
***USDA Nutrient Database, Minnesota Food and Nutrient Database (NDSR), Food product manufacturer, McCance and Widdowson's food table, Country-specific food tables, Other nutrient analysis (please specify)
****ONLY biomarker of interest for calcium is calcium balance

INTERVENTION(S), SKIP IF OBSERVATIONAL STUDY

UI	Author Year	Intervention(s)	Source (e.g., brand name, foods, or formulation)	Vit D and/or Ca Total Daily Dose	Intervention Duration	Intervention Frequency (e.g. capsules were taken 2 times a day)
Co-intervention(s) *:						
Compliance/Adherence:						

Duplicate one row per intervention, including control intervention.
*Report the non-vit D or Ca intervention(s) (e.g., other drug intervention, or background low-fat diet). We are interested in only independent effect of vitamin D and/or calcium. Therefore, describe how effects of co-intervention(s) were controlled for in the analyses or study design.

LIST OF ALL OUTCOMES

UI	Author Year	Primary / Secondary Outcome**	Outcome	Definition

Duplicate one row per outcome of interest. Only need to list outcomes that were included in the result section.
**Must have been explicitly stated in the original paper. Otherwise, please enter "nd"

UI	Author Year	Comments

Confounders: Please report all confounders controlled in the analyses reported in the following result section (adjusted results)

UI	Author Year	Confounder Groups	Please List Name of Confounder (including matching factors)	Specific comments for confounders
		Other nutrients or dietary factors (e.g., certain food consumption), including supplement use and total energy intake		
		Demographics (e.g., age, gender, race, education)?	Yes/no*	
		Anthropometrics (e.g., BMI, body weight, % body fat)?	Yes/no*	
		Medical conditions		
		Medication		
		Sunlight exposure and its proxy variables (e.g., seasonal variation of 25(OH)D, UV exposure, location)		
		Smoking and other life styles variables (e.g., physical activity, occupation, alcohol consumption)	Yes/no*	
		Other		

*Please choose "yes" if any one of the confounders in this group was controlled in the analysis

FOLLOWING IS RESULT SECTION. PLEASE CHOOSE APPROPRIATE TYPE OF DATA COLLECTION TABLE FOR ALL OUTCOMES OF INTEREST

Main Analyses (For analyses that adjusted for confounders, choose the "best" model)

2 ARMS/GROUPS: DICHOTOMOUS OUTCOMES (e.g. OR, RR, %death)

UI	Author Year	Outcome	Exposure/ Intervention	Mean Follow-up, mo	N Event	N Total	Outcome Metric (e.g. OR, RR, HR, %) and direction of comparison*	Unadjusted			Adjusted		
								Result	95% CI	P btw	Result	95% CI	P btw

*Example: OR Ca/placebo

2 ARMS/GROUPS: CONTINOUS OUTCOMES (e.g. BMD, BP)

UI	Author Year	Outcome	Unit	Exposure/ Intervention	Mean Follow-up, mo	No. Analyzed	Baseline	Baseline CI/SE/ SD*	Final or Delta**	Final or Delta CI/ SE/ SD*	Net difference	Net difference CI/SE/ SD*	P between

Baseline=baseline value; Final=final value; Delta=change value from baseline, which is Final-Baseline value; Net difference=differences in deltas
*Enter outcome metric reported in the unadjusted or adjusted result section
**Delta value is preferred than the Final value. Please report the direction for the change by using "+" or "-" sign: e.g. +2.8 or -2.8

≥2 ARMS/GROUPS: DICHOTOMOUS OUTCOMES (e.g. OR, RR, %death)

UI	Author Year	Outcome	Exposure Categories (e.g., Tertiles)/ Intervention Groups	Mean Vit D level/ dose	Mean Ca level/ dose	No. of Cases (Event)*	No. of Non-cases/ Total N**	Mean Follow-up, mo	Crude or Adjusted analysis?	Outcome Metric (e.g. OR, RR, HR, %)	Outcome effect size	CI/ SE/ SD**	P between groups***	P for trend****

Duplicate one row per exposure category or intervention group.
*Number of subjects with outcome
**Please choose one and delete the others
***Specify the comparison. For example group 1 vs. 3 = -6; group 1 vs. 2 = -8
****P value for testing the linear trend of the OR/RR across different categories or doses

≥2 ARMS/GROUPS: CONTINOUS OUTCOMES (e.g. BMD, BP)

UI	Author Year	Outcome	Unit	Exposure Category/ Intervention Group	Crude or Adjusted analysis?	Mean Follow-up (months)	No. Analyzed	Baseline	Baseline CI/SE/ SD*	Final or Delta**	Final or Delta CI/ SE/ SD*	Net difference***	Net difference CI/SE/ SD*	P between groups***

Duplicate one row per exposure category or intervention group. Please write "nd" if there was no data reported. DO NOT LEAVE BLANK.
*Please choose one and delete the others
**Delta value is preferred than the Final value. Please report the direction for the change by using "+" or "-" sign: e.g. +2.8 or -2.8
***Specify the comparison. For example group 1 vs. 3 = -6; group 1 vs. 2 = -8

MEAN DATA. THIS SHOULD ONLY APPLY TO CASE-COHORT STUDIES THAT COMPARE BASELINE VIT D / CA LEVELS BETWEEN CASES (WITH DISEASE) AND CONTROLS (WITHOUT DISEASE)

UI	Author Year	Outcome Group	Time between Baseline Exposure and Outcome Assessments	Crude or Adjusted analysis?	No. Analyzed	Mean 25(OH)D Level	Vit D level CI/SE/ SD*	Mean Ca intake or Ca balance	Ca CI/ SE/ SD*	P between groups
		Cases:								
		Control:								

Duplicate one table per outcome

OTHER RESULTS. ONLY USE THE FOLLOWING BOX WHEN THE TYPE OF RESULT DATA DO NOT FIT THE TABLES PROVIDED ABOVE

UI	Author Year	Outcome	Results

UI	Author Year	Comments for Results

Subgroup Analyses

Please copy the appropriate table above for all subgroup analyses of interest.

QUALITY of INTERVENTIONAL STUDIES

UI	Author Year	Design*	Appropriate Randomization Technique (y/n/nd/NA)	Allocation Concealment (y/n/nd/NA)	Appropriate Washout Period (y/n/nd/NA)	Dropout Rate <20%	Blinded Outcome Assessment (y/n/nd)	Intention to Treat Analysis (y/n/nd)	Appropriate Statistical Analysis** (y/n)	Assessment for Confounding (y/n/nd/NA)	Clear Reporting with No Discrepancies (y/n)	OVERALL Grade

Adverse Event(s): **	
Explanation for Overall Quality Grade (if not Grade A):	

NA=not applicable
***Please do not copy the 4 categories of study designs from above sections. Specify the exact study design: RCT – Parallel, RCT – Cross-over, RCT – Cluster, quasi-RCT, Non-randomized, but controlled trial, before-and-after trial, other interventional design (please explain in detail)**
****Please do not leave blank. Type nd if there was no data on adverse events.**

QUALITY of COHORT OR NESTED CASE-CONTROL STUDIES

UI	Author Year	Population	Exposure (All)	Dietary assessment*	Biomarkers*	Comparator	Statistical Analysis	Outcome	Design
		a) Eligibility criteria clear? (y/n)	a) Exposure assessor blinded to outcome info? (y/n)	a) Method reported? (y/n)	a) One of the prespecified methods*** was used? (y/n)	a) Level of the exposure in comparative categories (e.g., quartiles) is given (ranges)? (y/n) applicable for categorical analyses only	a) Adjusted or matched for ANY confounders (other than age and sex)?** (y/n)	a) Clear definition of outcome, including time of ascertainment? (y/n)	a) Prospective collection of data? (y/n)
		b) Sampling of population random or consecutive? (y/n)	b) Outcome assessor blinded to exposure measurement? (y/n)	b) Food composition database or suppl composition reported? (y/n)	Time from sample collection to sample analysis reported? (y/n)			b) Loss to follow-up <20%? (y/n)	b) Analysis was planned when cohort was formed? (y/n)
				c) Internal calibration of method perform (if FFQ)? (y/n/NA)			b) Justification of final adjusted model selection? (y/n)	c) Do the authors specify a primary outcome? (y/n)	c) Justification of sample size (includes sample size calculations)? (y/n)

OVERALL Grade (A/B/C):	
Explanation for Overall Quality Grade (if not Grade A):	

***Check "NA" and skip all questions if study did not use dietary assessment or biomarkers**
****We will judge in the end if the set of confounders is adequate**
*****Prespecified methods: HPLC, RIA kits, LC-MS/MS; EIA/Chemiluminescence**

Blank Data Extraction Form and Quality Assessment Checklists (From the Current Report)

Vitamin D Data Abstraction Form

Should this article have been previously excluded based on the exclusion criteria?

Select an Answer

- More than 20% of the population has a condition
- No outcome of interest
- Study design: Observational study of intermediate outcomes (cardiovascular and bone outcomes)
- Study design:SR/MA
- Study design other (please specify)
- Intervention: Other dietary supplements, not controlled for

Clear Response

Do you need another article to complete this form (i.e., data is reported in another article)?

- Yes (stop until the article is linked; specify reference number)
- No

Clear Response

Was this part of a trial?

We will be compiling all the studies per trial

- Yes (specify the trial name and stop)
- No Clear Response

Study Design

- ☐ RCT/CCT
- ☐ Prospective cohort
- ☐ Nested case control
- ☐ Post hoc

Population and Study Characteristics

Inclusion criteria for the study (check all that apply)

- ☐ 0-6 months
- ☐ 7 months-2 years
- ☐ 3-8 years
- ☐ 9-18 years
- ☐ 19-50 years
- ☐ 51-70 years
- ☐ ≥71 years
- ☐ Pregnant or lactating women
- ☐ Postmenopausal women
- ☐ Preterm newborns
- ☐ Healthy
- ☐ Persons with Osteopenia
- ☐ Able to participate, understand English..
- ☐ Other 1 (please specify) _____
- ☐ Other 2 (please specify) _____
- ☐ Other 3 (please specify) _____
- ☐ Other 4 (please specify) _____
- ☐ Other 5 (please specify) _____

☐ Other 6 (please specify) _____

☐ Other 7 (please specify) _____

☐ Not specified

Exclusion criteria for the study (check all that apply)

☐ Currently or previously taking vitamin d supplements (provide detail) _____

☐ Osteoporosis

☐ Other systemic bone disease (e.g., pagets)

☐ Prior fragility fracture

☐ Prior cancer

☐ Current cancer

☐ Current cardiovascular disease

☐ Hypertension

☐ Type 2 DM

☐ Pregnant

☐ Autoimmune disease

☐ Use of antihypertensives (provide details) _____

☐ Use of drugs related to bone metabolism (provide details) _____

☐ Use of medications that interfere with vitamin k (e.g., anticoagulants) (provide details) _____

☐ Consumption of dietary supplements (provide details) _____

☐ Prior cancer diagnosis (provide details) _____

☐ Prior CVD diagnosis (provide details) _____

☐ Other comobidity(ies)(provide details) _____

☐ Other 1 (specify) _____

☐ Other 2 (specify) _____

- ☐ Other 3 (specify) ____
- ☐ Other 4 (please specify) ____
- ☐ Other 5 (please specify) ____
- ☐ Other 6 (please specify) ____
- ☐ Other 7 (please specify) ____
- ☐ Not specified

Age (indicate the mean/range/SD of the control group)

- ☐ Mean age (indicate NR if not reported) ____
- ☐ Age range (indicate NR if not reported) ____
- ☐ Standard Deviation (if no age range was given) ____

Race/Ethnicity

- ☐ Non-Hispanic white (if % was given, please specify) ____
- ☐ Hispanic (if % was given, please specify) ____
- ☐ Non-Hispanic black (if % was given, please specify) ____
- ☐ Asian (if % was given, please specify) ____
- ☐ Mixed (if % was given, please specify) ____
- ☐ Race not specified (if % was given, please specify) ____
- ☐ Other_1 (specify and if % was given, please specify) ____
- ☐ Other_2 (specify and if % was given, please specify) ____
- ☐ Other_3 (specify and if % was given, please specify) ____
- ☐ Other_4 (specify and if % was given, please specify) ____
- ☐ Other_5 (specify and if % was given, please specify) ____
- ☐ NR (if % was given for an unknown group, please specify) ____

Countries

- ☐ Australia (specify city, if given) ____
- ☐ Canada (specify city, if given) ____
- ☐ China (specify city, if given) ____
- ☐ Finland (specify city, if given) ____
- ☐ Germany (specify city, if given) ____
- ☐ Turkey (specify city, if given) ____
- ☐ UK (specify city, if given) ____
- ☐ USA (specify city, if given) ____
- ☐ Multiple Countries
- ☐ Other (please specify) ____
- ☐ Not reported

Enrollment profile

- ☐ # Enrolled (indicate NR if not reported) ____
- ☐ % female (indicate NR if not reported) ____

Health and Nutritional status (check all that apply)

- ☐ Healthy
- ☐ Cancer in remission
- ☐ Osteopenia/Ibd
- ☐ Low birth weight/sga
- ☐ Preterm birth
- ☐ Vitamin D deficient/depleted
- ☐ Overweight/obese
- ☐ Malnourished/frailty
- ☐ Post menopausal
- ☐ Other ____
- ☐ Not Reported

Baseline vitamin D/calcium intake/level (if reported, indicate "NR" if not reported)

Interventions/exposures

- ☐ Supplemental vitamin D (none specified)
- ☐ Supplemental vitamin D2
- ☐ Supplemental vitamin D3
- ☐ Supplemental Calcium
- ☐ Vitamin D fortified food (amount per serving, amount per day)
- ☐ Serum vitamin D
- ☐ Serum vitamin D status categories (high vs. low, tertiles, quartiles, quintiles)
- ☐ Cord blood vitamin D
- ☐ Other (specify)

Sources [to be used in the arms table]:

Serum

D

D2

D3

Ca

D+Ca

D2+Ca

D3+Ca

Placebo

Arm 1/ Exposure 1	Source/ Blood level	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

Arm 2/ Exposure 2	Source/ Blood level	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

Arm 3/ Exposure 3	Source/ Blood level	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

Arm 4/ Exposure 4	Source/ Blood level	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

Arm 5/ Exposure 5	Source/Blo od level	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

Control 1	Source	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

Control 2	Source	Number of units	Units (e.g., mg, IU)	Frequency (1x, 2x)	Interval (e.g. per day)	Duration

---

What characteristics were the controls and cases matched on?

What confounders were controlled for in analyses

- ☐ Other nutrients or dietary factors (specify) ____
- ☐ Demographics (age, sex, race/ethnicity) (specify) ____
- ☐ Anthropometrics (specify) ____
- ☐ Medical conditions (specify) ____
- ☐ Sun exposure (specify) ____
- ☐ Smoking, other lifestyle factors (specify) ____
- ☐ Other 1 (specify) ____
- ☐ Other 2 (specify) ____
- ☐ Other 3 (specify) ____
- ☐ Other 4 (specify) ____
- ☐ Other 5 (specify) ____
- ☐ Other 6 (specify) ____
- ☐ Other 7 (specify) ____

What were the comparators?

- ☐ Placebo
- ☐ Not identified
- ☐ Other vitamin d dose (specify) ____
- ☐ Other (specify) ____

Compliance with treatment? (indicate % or number or indicate "NR" for not reported, and "NA" if there was no treatment)

Dose Response (check all that apply)

- ☐ Serum vitamin D
- ☐ Cord blood vitamin D
- ☐ Other (specify) _____

Autoimmune

- ☐ Colitis/Crohns
- ☐ Lupus
- ☐ Rheumatoid Arthritis
- ☐ Type 1 diabetes
- ☐ Other (specify) _____

Cancer

- ☐ Breast cancer
- ☐ Breast density
- ☐ Prostate cancer
- ☐ Colorectal adenoma (progression)
- ☐ Aberrant crypt cells
- ☐ Pancreatic cancer
- ☐ Any cancer mortality
- ☐ Other (specify) _____

Infections/Allergy/Asthma

- ☐ Infection-related mortality (specify) ☐
- ☐ Allergy (specify) ☐
- ☐ Asthma (specify) ☐
- ☐ Pediatric allergy (in child of woman who was subject of intervention/exposure) (specify) ☐
- ☐ Infectious process (specify) ☐
- ☐ Other (specify) ☐

Bone Health

- ☐ Osteoporotic/fragility fx
- ☐ Bone mineral density/content
- ☐ Rickets
- ☐ Falls
- ☐ Muscle strength
- ☐ Osteoporosis
- ☐ Other (specify) ☐

Cardiovascular outcomes

- ☐ Hypertension
- ☐ Cardiovascular disease
- ☐ Myocardial infarction
- ☐ Blood pressure change
- ☐ Cardiovascular disease mortality
- ☐ Other (specify) ☐

Pregnancy and/or Lactating Outcomes

- ☐ Premature birth
- ☐ Low birth weight/small for gestational age
- ☐ Pre-eclampsia
- ☐ Pregnancy hypertension
- ☐ Infant mortality
- ☐ Other (specify) _____

Adverse Events

- ☐ All-cause mortality
- ☐ Cancer mortality
- ☐ Renal outcomes
- ☐ Soft tissue calcification
- ☐ Other (specify) _____

Funding

- ☐ Government
- ☐ Private foundation
- ☐ Manufacturer
- ☐ Other (specify) _____
- ☐ Unclear

Have you reference mined this article?

- ● Yes (specify references needed to be checked) _____

- No

Clear Response

Has this form been checked by a second reviewer?

- Yes
- No Clear Response

Comments

QUALITY of INTERVENTIONAL STUDIES

Instructions: Y=Yes; N=No; ND=No Data; NA=not applicable

Study Design

- Parallel, RCT
- Cross-over, RCT
- Cluster, quasi-RCT
- Non-randomized, but controlled trial
- Before-and-after trial
- Other interventional design (please explain in detail)

Clear Response

Appropriate Randomization Technique

- Y
- N
- ND
- NA

Clear Response

Allocation Concealment

- Y
- N
- ND
- NA

Clear Response

Appropriate Washout Period

- Y
- N
- ND
- NA

Clear Response

Is the Dropout Rate <20%

- Y
- N
- ND

Clear Response

Blinded Outcome Assessment

- Y
- N
- ND

Clear Response

Intention to Treat Analysis

- Y
- N
- ND
- NA

Clear Response

Appropriate Statistical Analysis

- Y
- N

- ND

Clear Response

Assessment for Confounding

- Y
- N
- ND
- NA

Clear Response

Clear Reporting with No Discrepancies

- Y
- N

Clear Response

OVERALL Grade

- A
- B (explanation for overall quality grade)
- C (explanation for overall quality grade)

Clear Response

Comments

QUALITY of COHORT OR NESTED CASE-CONTROL STUDIES

Population

a) Eligibility criteria clear?

- Y
- N

Clear Response

b) Sampling of population random or consecutive?

- Y
- N

Clear Response

Exposure (All)

a) Exposure assessor blinded to outcome info?

- Y
- N

Clear Response

b) Outcome assessor blinded to exposure measurement?

- Y
- N

Clear Response

Dietary assessment*

*Check “NA” and skip all questions if study did not use dietary assessment or biomarkers

a) Method reported?

- Y
- N
- NA

Clear Response

b) Food composition database or suppl composition reported?

- Y
- N
- NA

Clear Response

c) Internal calibration of method perform (if FFQ)?

- Y
- N
- NA

Clear Response

Biomarkers*

*Check “NA” and skip all questions if study did not use dietary assessment or biomarkers

a) One of the prespecified methods* was used?

*Prespecified methods: HPLC, RIA kits, LC-MS/MS; EIA/Chemiluminescence

- Y
- N
- NA

Clear Response

b) Time from sample collection to sample analysis reported?

- Y
- N
- NA

Clear Response

Comparator

a) Level of the exposure in comparative categories (e.g., quartiles) is given (ranges)?*

*applicable for categorical analyses only

- Y
- N

Clear Response

Statistical Analysis

a) Adjusted or matched for ANY confounders (other than age and sex)?*

*We will judge in the end if the set of confounders is adequate

- Y
- N

Clear Response

b) Justification of final adjusted model selection?

- Y
- N

Clear Response

Outcome

a) Clear definition of outcome, including time of ascertainment?

- Y
- N

Clear Response

b) Loss to follow-up <20%?

- Y
- N

Clear Response

c) Do the authors specify a primary outcome?

- Y
- N
- NA

Clear Response

Design

a) Prospective collection of data?

- Y
- N

Clear Response

b) Analysis was planned when cohort was formed?

- Y
- N

Clear Response

c) Justification of sample size (includes sample size calculations)?

- Y

- N
- NA

Clear Response

OVERALL Grade (A/B/C):

- A
- B (explanation for overall quality grade)
- C (explanation for overall quality grade)

Clear Response

Comments

Appendix F. Excluded Studies

Excluded Studies (From the Original Report)

Excluded Study	Reason
Aalberts JS, Weegels PL, van der HL et al. Calcium supplementation: effect on blood pressure and urinary mineral excretion in normotensive male lactoovovegetarians and omnivores. American Journal of Clinical Nutrition 48 (1):131-8, 1988.	No outcomes of interest
Abbasi AA, Chemplavil JK, Farah S, Muller BF, Arnstein AR. Hypercalcemia in active pulmonary tuberculosis. Annals of Internal Medicine 90 (3):324-8, 1979.	No UL outcomes
Abrams SA, Griffin IJ, Hawthorne KM, Ellis KJ. Effect of prebiotic supplementation and calcium intake on body mass index. Journal of Pediatrics 2007; 151(3):293-298.	Not a calcium intervention trial
Adams JS, Lee G. Gains in bone mineral density with resolution of Vitamin D intoxication. Annals of Internal Medicine 127 (3):203-6, 1997.	Case report
Akcakus M, Koklu E, Budak N, Kula M, Kurtoglu S, Koklu S. The relationship between birthweight, 25-hydroxyVitamin D concentrations and bone mineral status in neonates. Annals of Tropical Paediatrics 2006; 26(4):267-275.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Ala-Houhala M, Koskinen T, Terho A, Koivula T, Visakorpi J. Maternal compared with infant Vitamin D supplementation. Archives of Disease in Childhood 61 (12):1159-63, 1986.	Not RCT arrow 4 study
Ala-Houhala M. 25-HydroxyVitamin D levels during breast-feeding with or without maternal or infantile supplementation of Vitamin D. Journal of Pediatric Gastroenterology & Nutrition 4(2):220-6, 1985.	In Ottawa EPC report
Almendingen K, Hofstad B, Vatn MH. Dietary habits and growth and recurrence of colorectal adenomas: results from a three-year endoscopic follow-up study. Nutrition & Cancer 49 (2):131-8, 2004.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Almendingen K, Hofstad B, Vatn MH. Lifestyle-related factors and colorectal polyps: preliminary results from a Norwegian follow-up and intervention study. European Journal of Cancer Prevention 11(2):153-8, 2002.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Almendingen K, Trygg K, Hofstad B, Veierod MB, Vatn MH. Results from two repeated 5 day dietary records with a 1 y interval among patients with colorectal polyps. European Journal of Clinical Nutrition 55 (5):374-9, 2001.	No outcomes of interest
Al-oanzi ZH, Tuck SP, Raj N et al. Assessment of Vitamin D status in male osteoporosis. Clinical Chemistry 52 (2):248-54, 2006.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Aloia JF, Talwar SA, Pollack S, Feuerman M, Yeh JK. Optimal Vitamin D status and serum parathyroid hormone concentrations in African American women. American Journal of Clinical Nutrition 84 (3):602-9, 2006.	No outcomes of interest
Anonymous. Calcium supplementation during pregnancy reduces the risk of developing preeclampsia in nulliparous women. Canadian Family Physician 45:614, 618-20, 1999.	Editorial-like brief review
Anonymous. Vitamin D supplementation for northern native communities. Indian and Inuit Health Committee, Canadian Paediatric Society. CMAJ Canadian Medical Association Journal 138 (3):229-30, 1988.	Review paper
Armitage NC, Rooney PS, Gifford KA, Clarke PA, Hardcastle JD. The effect of calcium supplements on rectal mucosal proliferation. British Journal of Cancer 71 (1):186-90, 1995.	No outcomes of interest
Armstrong AL, Oborne J, Coupland CA, Macpherson MB, Bassey EJ, Wallace WA. Effects of hormone replacement therapy on muscle performance and balance in post-menopausal women. Clinical Science 91 (6):685 -90, 1996.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Arunabh S, Pollack S, Yeh J, Aloia JF. Body fat content and 25-hydroxyVitamin D levels in healthy women. Journal of Clinical Endocrinology & Metabolism 88 (1):157-61, 2003.	Cross-sectional or retrospective assessment of diet after disease diagnosis
August P, Helseth G, Cook EF, Sison C. A prediction model for superimposed preeclampsia in women with chronic hypertension during pregnancy. American Journal of Obstetrics & Gynecology. 191(5):1666-72, 2004 Nov.	>=20% subjects with diseases

Excluded Study	Reason
August P, Marcaccio B, Gertner JM, Druzin ML, Resnick LM, Laragh JH. Abnormal 1,25-dihydroxyVitamin D metabolism in preeclampsia. American Journal of Obstetrics & Gynecology 166 (4):1295-9, 1992.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Back O, Blomquist HK, Hernell O, Stenberg B. Does vitamin D intake during infancy promote the development of atopic allergy? Acta Dermato - Venereologica 89 (1):28 -32, 2009.	combination of vit D/Ca and other treatment w/o analysis of independent effect
Bailey BW, Sullivan DK, Kirk EP, Hall S, Donnelly JE. The influence of calcium consumption on weight and fat following 9 months of exercise in men and women. Journal of the American College of Nutrition 2007; 26(4):350-355.	No outcomes of interest
Bakker R, Rifas-Shiman SL, Kleinman KP, Lipshultz SE, Gillman MW. Maternal calcium intake during pregnancy and blood pressure in the offspring at age 3 years: a follow-up analysis of the Project Viva cohort. American Journal of Epidemiology 168 (12):1374 -80, 2008.	age <18 (BP outcome)
Baron JA, Beach M, Mandel JS et al. Calcium supplements and colorectal adenomas. Polyp Prevention Study Group. Annals of the New York Academy of Sciences 889:138-45, 1999.	Duplicate publication (see Baron 1999 NEJM)
Baron JA, Beach M, Mandel JS et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. New England Journal of Medicine 340 (2):101-7, 1999.	In Weigarten 2008 systematic review
Baron JA, Tosteson TD, Wargovich MJ et al. Calcium supplementation and rectal mucosal proliferation: a randomized controlled trial. Journal of the National Cancer Institute 87 (17):1303-7, 1995.	No outcomes of interest
Barr SI. Calcium and body fat in peripubertal girls: cross-sectional and longitudinal observations. Obesity 2007; 15(5):1302-1310.	Not RCT growth study
Barsoum GH, Hendrickse C, Winslet MC et al. Reduction of mucosal crypt cell proliferation in patients with colorectal adenomatous polyps by dietary calcium supplementation. British Journal of Surgery 79 (6):581-3, 1992.	No outcomes of interest
Basile LA, Taylor SN, Wagner CL, Horst RL, Hollis BW. The effect of high-dose Vitamin D supplementation on serum Vitamin D levels and milk calcium concentration in lactating women and their infants. Breastfeeding Medicine: The Official Journal of the Academy of Breastfeeding Medicine 2006; 1(1):27-35.	In Ottawa EPC report
Belizan JM, Villar J, Bergel E et al. Long-term effect of calcium supplementation during pregnancy on the blood pressure of offspring: follow up of a randomised controlled trial.. BMJ 315 (7103):281-5, 1997.	In Hofmeyer 2007 systematic review
Belizan JM, Villar J, Gonzalez L, Campodonico L, Bergel E. Calcium supplementation to prevent hypertensive disorders of pregnancy.. New England Journal of Medicine 325 (20):1399 -405, 1991.	In Hofmeyer 2007 systematic review
Belizan JM, Villar J, Pineda O et al. Reduction of blood pressure with calcium supplementation in young adults. JAMA 249 (9):1161 -5, 1983.	In systematic review
Belizan JM, Villar J, Zalazar A, Rojas L, Chan D, Bryce GF. Preliminary evidence of the effect of calcium supplementation on blood pressure in normal pregnant women. American Journal of Obstetrics & Gynecology 146 (2):175 -80, 1983.	In Hofmeyer 2007 systematic review
Bell NH, Epstein S, Greene A, Shary J, Oexmann MJ, Shaw S. Evidence for alteration of the Vitamin D-endocrine system in obese subjects. Journal of Clinical Investigation 76 (1):370-3, 1985.	Not RCT arrow 4 study
Bell NH, Epstein S, Shary J, Greene V, Oexmann MJ, Shaw S. Evidence of a probable role for 25-hydroxyVitamin D in the regulation of human calcium metabolism. Journal of Bone & Mineral Research 3(5):489-95, 1988.	Not RCT arrow 4 study
Bell NH, Godsen RN, Henry DP, Shary J, Epstein S. The effects of muscle-building exercise on Vitamin D and mineral metabolism. Journal of Bone & Mineral Research 3(4):369-73, 1988.	No outcomes of interest
Bell NH. Hypercalcemic and hypocalcemic disorders: diagnosis and treatment. Nephron 23(2-3):147-51, 1979.	Review paper
Berggren M, Stenvall M, Olofsson B, Gustafson Y. Evaluation of a fall-prevention program in older people after femoral neck fracture: a one-year follow-up. Osteoporosis International 1919;801-9.	100% patients with femoral neck fracture who admitted to the hospital
Berkey CS, Rockett HR, Willett WC, Colditz GA. Milk, dairy fat, dietary calcium, and weight gain: a longitudinal study of adolescents.. Archives of Pediatrics & Adolescent Medicine 159 (6):543 -50, 2005.	Not RCT growth study

Excluded Study	Reason
Berube S, Diorio C, Masse B et al. Vitamin D and calcium intakes from food or supplements and mammographic breast density. Cancer Epidemiology, Biomarkers & Prevention 14(7):1653-9, 2005.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Bierenbaum ML, Fleischman AI, Raichelson RI. Long term human studies on the lipid effects of oral calcium. Lipids 7 (3):202-6, 1972.	No outcomes of interest
Bierenbaum ML, Wolf E, Bisgeier G, Maginnis WP. Dietary calcium. A method of lowering blood pressure. American Journal of Hypertension 1(3 Pt 3):149S - 152S, 1988.	In systematic review
Bischoff HA, Stahelin HB, Dick W et al. Effects of Vitamin D and calcium supplementation on falls: a randomized controlled trial.. Journal of Bone & Mineral Research 18 (2):343-51, 2003.	In Ottawa EPC report
Bischoff-Ferrari HA, Conzelmann M, Stahelin HB et al. Is fall prevention by Vitamin D mediated by a change in postural or dynamic balance? Osteoporosis International 2006; 17(5):656-663.	Secondary analysis of an original RCT by Bischoff-Ferrari 2003, which is already in Ottawa's report
Bischoff-Ferrari HA, Orav EJ, wson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. Archives of Internal Medicine 166 (4):424-30, 2006.	In Ottawa EPC report
Blum M, Kirsten M, Worth MH, Jr. Reversible hypertension. Caused by the hypercalcemia of hyperparathyroidism, Vitamin D toxicity, and calcium infusion. JAMA 237 (3):262 -3, 1977.	No 25(OH)D or dietary Ca
Boggess KA, Samuel L, Schmucker BC, Waters J, Easterling TR. A randomized controlled trial of the effect of third-trimester calcium supplementation on maternal hemodynamic function. Obstetrics & Gynecology 90 (2):157-61, 1997.	In Hofmeyer 2007 systematic review
Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, Faivre J. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. European Cancer Prevention Organisation Study Group. Lancet 356 (9238):1300-6, 2000.	In Weigarten 2008 systematic review
Bonithon-Kopp C, Piard F, Fenger C et al. Colorectal adenoma characteristics as predictors of recurrence. Diseases of the Colon & Rectum 47 (3):323-33, 2004.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Boon N, Koppes LL, Saris WH, Van MW. The relation between calcium intake and body composition in a Dutch population: The Amsterdam Growth and Health Longitudinal Study. American Journal of Epidemiology 162 (1):27-32, 2005.	No outcomes of interest
Bostick RM, Fosdick L, Grandits GA, Grambsch P, Gross M, Louis TA. Effect of calcium supplementation on serum cholesterol and blood pressure. A randomized, double-blind, placebo-controlled, clinical trial. Archives of Family Medicine 9(1):31-8 2000.	>=20% subjects with diseases
Bostick RM, Fosdick L, Wood JR et al. Calcium and colorectal epithelial cell proliferation in sporadic adenoma patients: a randomized, double-blinded, placebo-controlled clinical trial.. Journal of the National Cancer Institute 87 (17):1307-15, 1995.	No outcomes of interest
Bostick RM, Potter JD, Fosdick L et al. Calcium and colorectal epithelial cell proliferation: a preliminary randomized, double-blinded, placebo-controlled clinical trial. Journal of the National Cancer Institute. 85(2):132-41, 1993 Jan 20.	No outcomes of interest
Boutron MC, Faivre J, Marteau P, Couillault C, Senesse P, Quipourt V. Calcium, phosphorus, Vitamin D, dairy products and colorectal carcinogenesis: a French case--control study.. British Journal of Cancer 74 (1):145-51, 1996.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Bowen J, Noakes M, Clifton PM. Effect of calcium and dairy foods in high protein, energy-restricted diets on weight loss and metabolic parameters in overweight adults. International Journal of Obesity 29 (8):957-65, 2005.	In systematic review
Braverman AS. Evidence that high calcium and Vitamin D intake decrease the risk of breast cancer in premenopausal women: implications for breast cancer prevention and screening. Southern Medical Journal 100 (11):1061-2, 2007.	Review paper
Brekke HK, Ludvigsson J. Vitamin D supplementation and diabetes-related autoimmunity in the ABIS study. Pediatric Diabetes 2007; 8(1):11-14.	No 25(OH)D or dietary Ca
Broe KE, Chen TC, Weinberg J, Bischoff-Ferrari HA, Holick MF, Kiel DP. A higher dose of Vitamin d reduces the risk of falls in nursing home residents: a randomized, multiple-dose study. Journal of the American Geriatrics Society 2007; 55(2):234-239.	In Ottawa EPC report

Excluded Study	Reason
Brooke OG, Butters F, Wood C. Intrauterine Vitamin D nutrition and postnatal growth in Asian infants. British Medical Journal Clinical Research Ed 283 (6298):1024, 1981.	No 25(OH)D or dietary Ca
Brooke OG. Supplementary Vitamin D in infancy and childhood. Archives of Disease in Childhood 1983; 58(8):573-574.	Review paper
Brunvand L, Quigstad E, Urdal P, Haug E. Vitamin D deficiency and fetal growth. Early Human Development 45 (1-2):27-33, 1996.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Brunvand L, Shah SS, Bergstrom S, Haug E. Vitamin D deficiency in pregnancy is not associated with obstructed labor. A study among Pakistani women in Karachi. Acta Obstetricia et Gynecologica Scandinavica 77 (3):303-6, 1998.	No outcomes of interest
Campbell CG, Chew BP, Luedecke LO, Shultz TD. Yogurt consumption does not enhance immune function in healthy premenopausal women. Nutrition & Cancer 37 (1):27-35, 2000.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Cancela L, Le BN, Miravet L. Relationship between the Vitamin D content of maternal milk and the Vitamin D status of nursing women and breast-fed infants. Journal of Endocrinology 110 (1):43-50, 1986.	Not RCT arrow 4 study
Canto-Costa MH, Kunii I, Hauache OM. Body fat and cholecalciferol supplementation in elderly homebound individuals. Brazilian Journal of Medical & Biological Research 39 (1):91-8, 2006.	Not RCT arrow 4 study
Caplan RH, Miller CD, Silva PD. Severe hypercalcemia in a lactating woman in association with moderate calcium carbonate supplementation: a case report. Journal of Reproductive Medicine 49 (3):214-7, 2004.	Case report
Cappuccio FP, Elliott P, Allender PS, Pryer J, Follman DA, Cutler JA. Epidemiologic association between dietary calcium intake and blood pressure: a meta-analysis of published data. American Journal of Epidemiology 142 (9):935-45, 1995.	Meta-analysis
Carlon GC, Howland WS, Goldiner PL, Kahn RC, Bertoni G, Turnbull AD. Adverse effects of calcium administration. Report of two cases. Archives of Surgery 113 (7):882-5, 1978.	Case report
Carlson LA, Derblom H, Lanner A. Effect of different doses of Vitamin D on serum cholesterol and triglyceride levels in healthy men. Atherosclerosis 12 (2):313-7, 1970.	Multiple antioxidant trials analyses
Caruso JB, Patel RM, Julka K, Parish DC. Health-behavior induced disease: return of the milk-alkali syndrome. Journal of General Internal Medicine 2007; 22(7):1053-1055.	Case report
Cats A, Kleibeuker JH, van der MR et al. Randomized, double-blinded, placebo-controlled intervention study with supplemental calcium in families with hereditary nonpolyposis colorectal cancer. Journal of the National Cancer Institute 87 (8):598-603, 1995.	No outcomes of interest
Cervellin G, Bonino P, Palummeri E, Passeri M. Calcium phosphate and blood pressure: their relationships in a geriatric population. American Journal of Nephrology 6 Suppl 1:16-8, 1986.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Chan GM, Roberts CC, Folland D, Jackson R. Growth and bone mineralization of normal breast-fed infants and the effects of lactation on maternal bone mineral status. American Journal of Clinical Nutrition 36 (3):438-43, 1982.	In Ottawa EPC report
Chan GM. Growth and bone mineral status of discharged very low birth weight infants fed different formulas or human milk. Journal of Pediatrics 123 (3):439-43, 1993.	>=20% subjects with diseases
Chan JM, Pietinen P, Virtanen M et al. Diet and prostate cancer risk in a cohort of smokers, with a specific focus on calcium and phosphorus (Finland). Cancer Causes & Control 11(9):859-67, 2000.	Superseded by Mitrou 2007
Chen W, Dawsey SM, Qiao YL et al. Prospective study of serum 25(OH)-Vitamin D concentration and risk of oesophageal and gastric cancers. British Journal of Cancer 2007; 97(1):123-128.	No outcomes of interest
Chyou PH, Nomura AM, Stemmermann GN. Diet, alcohol, smoking and cancer of the upper aerodigestive tract: a prospective study among Hawaii Japanese men. International Journal of Cancer 60 (5):616-21, 1995.	No outcomes of interest
Cleghorn GJ, Tudehope DI. Neonatal intestinal obstruction associated with oral calcium supplementation. Australian Paediatric Journal 17(4):298-9, 1981.	Case report

Excluded Study	Reason
Cockburn F, Belton NR, Purvis RJ et al. Maternal Vitamin D intake and mineral metabolism in mothers and their newborn infants. British Medical Journal 281 (6232):11-4, 1980.	Not RCT arrow 4 study
Cohen GR, Curet LB, Levine RJ et al. Ethnicity, nutrition, and birth outcomes in nulliparous women. American Journal of Obstetrics & Gynecology 2001; 185(3):660-667.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Colditz GA, Manson JE, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Diet and risk of clinical diabetes in women. American Journal of Clinical Nutrition 55 (5):1018 -23, 1992.	No outcomes of interest
Combs GF, Jr., Hassan N, Dellagana N et al. Apparent efficacy of food-based calcium supplementation in preventing rickets in Bangladesh. Biological Trace Element Research 121 (3):193 -204, 2008.	>=20% subjects with diseases
Cong K, Chi S, Liu G. Calcium supplementation during pregnancy for reducing pregnancy induced hypertension. Chinese Medical Journal 108 (1):57-9, 1995.	In Hofmeyer 2007 systematic review
Corless D, Dawson E, Fraser F et al. Do Vitamin D supplements improve the physical capabilities of elderly hospital patients? Age & Ageing 14(2):76-84, 1985.	In Ottawa EPC report
Cosman F, Nieves J, Shen V, Lindsay R. Oral 1,25-dihydroxyVitamin D administration in osteoporotic women: effects of estrogen therapy. Journal of Bone & Mineral Research 10(4):594-600, 1995.	Not RCT arrow 4 study
Costenbader KH, Feskanich D, Holmes M, Karlson EW, ito-Garcia E. Vitamin D intake and risks of systemic lupus erythematosus and rheumatoid arthritis in women. Annals of the Rheumatic Diseases 67 (4):530-5, 2008.	Observational study estimated Vitamin D supplement doses
Crowther CA, Hiller JE, Pridmore B et al. Calcium supplementation in nulliparous women for the prevention of pregnancy-induced hypertension, preeclampsia and preterm birth: an Australian randomized trial. FRACOG and the ACT Study Group. Australian & New Zealand Journal of Obstetrics & Gynaecology 39 (1):12-8, 1999.	In Hofmeyer 2007 systematic review
Dahifar H, Faraji A, Yassobi S, Ghorbani A. Asymptomatic rickets in adolescent girls. Indian Journal of Pediatrics 2007; 74(6):571-575.	Not RCT arrow 4 study
Dattani JT, Exton-Smith AN, Stephen JM. Vitamin D status of the elderly in relation to age and exposure to sunlight. Human Nutrition - Clinical Nutrition 38 (2):131-7, 1984.	Not RCT arrow 4 study
Dauchet L, Kesse-Guyot E, Czernichow S et al. Dietary patterns and blood pressure change over 5-y follow-up in the SU.VI.MAX cohort. American Journal of Clinical Nutrition 2007; 85(6):1650-1656.	No 25(OH)D or dietary Ca
Davie MW, Abraham RR, Hewins B, Wynn V. Changes in bone and muscle constituents during dieting for obesity. Clinical Science 70 (3):285-93, 1986.	No outcomes of interest
Davies KM, Heaney RP, Recker RR et al. Calcium intake and body weight. Journal of Clinical Endocrinology & Metabolism 85 (12):4635-8, 2000.	Meta-analysis; five clinical studies
Deheeger M, Bellisle F, Rolland-Cachera MF. The French longitudinal study of growth and nutrition: data in adolescent males and females. Journal of Human Nutrition & Dietetics 15 (6):429-38, 2002.	Analysis did not relate exposure to outcome
DeJongh ED, Binkley TL, Specker BL. Fat mass gain is lower in calcium-supplemented than in unsupplemented preschool children with low dietary calcium intakes. American Journal of Clinical Nutrition 84 (5):1123-7, 2006.	<9y (a study on BMI)
Dent CE, Gupta MM. Plasma 25-hydroxyVitamin-D-levels during pregnancy in Caucasians and in vegetarian and non-vegetarian Asians. Lancet 2(7944):1057-60, 1975.	No outcomes of interest
DeSantiago S, Alonso L, Halhali A, Larrea F, Isoard F, Bourges H. Negative calcium balance during lactation in rural Mexican women. American Journal of Clinical Nutrition 76 (4):845-51, 2002.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Devereux G, Litonjua AA, Turner SW et al. Maternal Vitamin D intake during pregnancy and early childhood wheezing. American Journal of Clinical Nutrition 2007; 85(3):853-859.	No 25(OH)D or dietary Ca
Dewey KG, Lonnerdal B. Milk and nutrient intake of breast-fed infants from 1 to 6 months: relation to growth and fatness. Journal of Pediatric Gastroenterology & Nutrition 2(3):497 -506, 1983.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Dhesi JK, Bearne LM, Moniz C et al. Neuromuscular and psychomotor function in elderly subjects who fall and the relationship with Vitamin D status. Journal of Bone & Mineral Research 17(5):891-7, 2002.	Cross-sectional or retrospective assessment of diet after disease diagnosis

Excluded Study	Reason
Dhesi JK, Jackson SH, Bearne LM et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age & Ageing 33 (6):589-95, 2004.	Intramuscular injection of high dose ergocalciferol
Dijkstra SH, van BA, Janssen JW, de Vleeschouwer LH, Huysman WA, van den Akker EL. High prevalence of Vitamin D deficiency in newborn infants of high-risk mothers.[erratum appears in Arch Dis Child. 2007 Nov;92(11):1049]. Archives of Disease in Childhood 2007; 92(9):750-753.	Relationship between mother's 25(OH)D and infant's 25(OH)D levels
Dixon LB, Pellizzon MA, Jawad AF, Tershakovec AM. Calcium and dairy intake and measures of obesity in hyper- and normocholesterolemic children. Obesity Research 13(10):1727-38, 2005.	Outcome is BW but participants age is from 4 to 10y (mostly <9y)
Dobnig H, Pilz S, Scharnagl H et al. Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. Archives of Internal Medicine 168 (12):1340 -9, 2008.	>=20% subjects with diseases
Doege C, Bauer J. Effect of high volume intake of mother's milk with an individualized supplementation of minerals and protein on early growth of preterm infants <28 weeks of gestation. Clinical Nutrition 26 (5):581-8, 2007.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Domrongkitchaiporn S, Ongphiphadhanakul B, Stitchantrakul W et al. Risk of calcium oxalate nephrolithiasis after calcium or combined calcium and calcitriol supplementation in postmenopausal women. Osteoporosis International 11(6):486-92, 2000.	No outcomes of interest, no UL outcomes
Drinka PJ, Nolten WE. Hazards of treating osteoporosis and hypertension concurrently with calcium, Vitamin D, and distal diuretics. Journal of the American Geriatrics Society 32 (5):405-7, 1984.	Case report
Drouillet P, Balkau B, Charles MA et al. Calcium consumption and insulin resistance syndrome parameters. Data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR). Nutrition Metabolism & Cardiovascular Diseases 2007; 17(7):486-492.	No outcomes of interest
Ehrenberg A. Non-medical prevention of pre-eclampsia. Acta Obstetricia et Gynecologica Scandinavica - Supplement 164:108-10, 1997.	Review paper
Epstein S, Bell NH, Shary J, Shaw S, Greene A, Oexmann MJ. Evidence that obesity does not influence the Vitamin D-endocrine system in blacks. Journal of Bone & Mineral Research 1(2):181-4, 1986.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Epstein S, Stern PH, Bell NH, Dowdeswell I, Turner RT. Evidence for abnormal regulation of circulating 1 alpha, 25-dihydroxyVitamin D in patients with pulmonary tuberculosis and normal calcium metabolism. Calcified Tissue International 36 (5):541-4, 1984.	Not RCT arrow 4 study
Ertbeg P, Norgaard P, Bang L, Nyholm H, Rudnicki M. Ionized magnesium in gestational diabetes. Magnesium Research 17(1):35-8, 2004.	No 25(OH)D or dietary Ca
Faivre J, Couillault C, Kronborg O et al. Chemoprevention of metachronous adenomas of the large bowel: design and interim results of a randomized trial of calcium and fibre. ECP Colon Group. European Journal of Cancer Prevention 6(2):132-8, 1997.	Design and interim results article
Farrerons J, Barnadas M, Rodriguez J et al. Clinically prescribed sunscreen (sun protection factor 15) does not decrease serum Vitamin D concentration sufficiently either to induce changes in parathyroid function or in metabolic markers. British Journal of Dermatology 139 (3):422-7, 1998.	No outcomes of interest
Faulkner KA, Cauley JA, Zmuda JM et al. Higher 1,25-dihydroxyVitamin D3 concentrations associated with lower fall rates in older community-dwelling women. Osteoporosis International 2006; 17(9):1318-1328.	In Ottawa EPC report
Feeley RM, Eitenmiller RR, Jones JB, Jr., Barnhart H. Calcium, phosphorus, and magnesium contents of human milk during early lactation. Journal of Pediatric Gastroenterology & Nutrition 2(2):262-7, 1983.	No outcomes of interest
Felson DT, Niu J, Clancy M et al. Low levels of Vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies. Arthritis & Rheumatism 2007; 56(1):129-136.	No outcomes of interest
Fleischman AR, Rosen JF, Cole J, Smith CM, DeLuca HF. Maternal and fetal serum 1,25-dihydroxyVitamin D levels at term. Journal of Pediatrics 1980; 97(4):640-642.	No outcomes of interest
Fleischman AR, Rosen JF, Nathenson G. 25-hydroxyVitamin D. Serum levels and oral administration of calcifediol in neonates. Archives of Internal Medicine 138 Spec No: 869-73, 1978.	Premature infants

Excluded Study	Reason
Forman JP, Bischoff-Ferrari HA, Willett WC, Stampfer MJ, Curhan GC. Vitamin D intake and risk of incident hypertension: results from three large prospective cohort studies. Hypertension 46 (4):676-82, 2005.	No 25(OH)D or dietary Ca
Franco A, Sikalidis AK, Solis Herruzo JA. Colorectal cancer: influence of diet and lifestyle factors. Revista Espanola de Enfermedades Digestivas 97 (6):432-48, 2005.	Review paper
Freedman DM, Tangrea JA, Virtamo J, Albanes D. The effect of beta-carotene supplementation on serum Vitamin D metabolite concentrations. Cancer Epidemiology, Biomarkers & Prevention 8 (12):1115-6, 1999.	No outcomes of interest
Fronczak CM, Baron AE, Chase HP et al. In utero dietary exposures and risk of islet autoimmunity in children. Diabetes Care 26 (12):3237 -42, 2003.	Observational study estimated Vitamin D supplement doses
Galloe AM, Graudal N, Moller J, Bro H, Jorgensen M, Christensen HR. Effect of oral calcium supplementation on blood pressure in patients with previously untreated hypertension: a randomised, double-blind, placebo-controlled, crossover study. Journal of Human Hypertension 7 (1):43-5, 1993.	In systematic review
Gambacciani M, Ciaponi M, Cappagli B et al. Body weight, body fat distribution, and hormonal replacement therapy in early postmenopausal women.[erratum appears in J Clin Endocrinol Metab 1997 Dec;82(12):4074]. Journal of Clinical Endocrinology & Metabolism 82 (2):414-7, 1997.	No outcomes of interest
Garland CF, Garland FC. Do sunlight and Vitamin D reduce the likelihood of colon cancer? [reprint in Int J Epidemiol. 2006 Apr;35(2):217-20; PMID: 16303809]. International Journal of Epidemiology 9 (3):227-31, 1980.	Ecological study
Garland CF, Mohr SB, Gorham ED, Grant WB, Garland FC. Role of ultraviolet B irradiance and Vitamin D in prevention of ovarian cancer. American Journal of Preventive Medicine 2006; 31(6):512-514.	No 25(OH)D or dietary Ca
Genkinger JM, Hunter DJ, Spiegelman D et al. Dairy products and ovarian cancer: a pooled analysis of 12 cohort studies. Cancer Epidemiology, Biomarkers & Prevention 15 (2):364-72, 2006.	Pooled analysis
Gertner JM, Domenech M. 25-HydroxyVitamin D levels in patients treated with high-dosage ergo- and cholecalciferol. Journal of Clinical Pathology 30(2):144-50, 1977.	>=20% subjects with diseases
Gillies DR, Hay A, Sheltawy MJ, Congdon PJ. Effect of phototherapy on plasma 25(OH)-Vitamin D in neonates. Biology of the Neonate 1984; 45(5):225-227.	Not RCT arrow 4 study
Gillman MW, Oliveria SA, Moore LL, Ellison RC. Inverse association of dietary calcium with systolic blood pressure in young children. JAMA 267 (17):2340-3, 1992.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Gillman MW, Rifas-Shiman SL, Kleinman KP, Rich-Edwards JW, Lipshultz SE. Maternal calcium intake and offspring blood pressure. Circulation 110 (14):1990-5, 2004.	Relationship between maternal intake and offspring blood pressure
Giovannucci E, Liu Y, Rimm EB et al. Prospective study of predictors of Vitamin D status and cancer incidence and mortality in men.. Journal of the National Cancer Institute 98 (7):451-9, 2006.	Superseded by Giovannucci 2007
Giovannucci E, Rimm EB, Wolk A et al. Calcium and fructose intake in relation to risk of prostate cancer. Cancer Research 58 (3):442-7, 1998.	Predictive model was used to predict 25(OH)D levels of whole cohort
Giovannucci E, Stampfer MJ, Colditz GA et al. MultiVitamin use, folate, and colon cancer in women in the Nurses' Health Study.. Annals of Internal Medicine 129 (7):517 -24, 1998.	No 25(OH)D or dietary Ca
Gonzalez AJ, White E, Kristal A, Littman AJ. Calcium intake and 10-year weight change in middle-aged adults. Journal of the American Dietetic Association 106 (7):1066-73 2006.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Goswami R, Gupta N, Ray D, Singh N, Tomar N. Pattern of 25-hydroxy vitamin D response at short (2 month) and long (1 year) interval after 8 weeks of oral supplementation with cholecalciferol in Asian Indians with chronic hypovitaminosis D. British Journal of Nutrition 100 (3):526-9, 2008.	not RCT curve 4 study
Grady D, Halloran B, Cummings S et al. 1,25-DihydroxyVitamin D3 and muscle strength in the elderly: a randomized controlled trial. Journal of Clinical Endocrinology & Metabolism 73 (5):1111-7, 1991.	1,25(OH)2D supplement
Grant WB. The likely role of Vitamin D from solar ultraviolet-B irradiance in increasing cancer survival. Anticancer Research 26 (4A):2605-14, 2006.	Ecological study

Excluded Study	Reason
Grau MV, Baron JA, Barry EL et al. Interaction of calcium supplementation and nonsteroidal anti-inflammatory drugs and the risk of colorectal adenomas. Cancer Epidemiology, Biomarkers & Prevention 14(10):2353-8, 2005.	In Weigarten 2008 systematic review
Greene MF. Trial of calcium to prevent preeclampsia. Journal of Women's Health 6(4):485-6, 1997.	Commentary
Greer FR, Ho M, Dodson D, Tsang RC. Lack of 25-hydroxyVitamin D and 1,25-dihydroxyVitamin D in human milk. Journal of Pediatrics 99 (2):233-5, 1981.	No 25(OH)D or dietary Ca
Greer FR, Hollis BW, Cripps DJ, Tsang RC. Effects of maternal ultraviolet B irradiation on Vitamin D content of human milk. Journal of Pediatrics 105 (3):431-3, 1984.	No 25(OH)D or dietary Ca
Greer FR, Marshall S. Bone mineral content, serum Vitamin D metabolite concentrations, and ultraviolet B light exposure in infants fed human milk with and without Vitamin D2 supplements. Journal of Pediatrics 114 (2):204-12, 1989.	In Ottawa EPC report
Greer FR, Searcy JE, Levin RS, Steichen JJ, Asch PS, Tsang RC. Bone mineral content and serum 25-hydroxyVitamin D concentration in breast-fed infants with and without supplemental Vitamin D. Journal of Pediatrics 98 (5):696-701, 1981.	In Ottawa EPC report
Gruson M, Cancela L, Denne MA, Miravet L. Relationship between bone GLA-protein (BGP) and calcidiol (25-hydroxycalciferol) in serum of breast-fed infants. Endocrinologia Experimentalis. 20(2-3):329-34, 1986 Aug.	25(OH)D supplement
Gunther CW, Legowski PA, Lyle RM et al. Dairy products do not lead to alterations in body weight or fat mass in young women in a 1-y intervention. American Journal of Clinical Nutrition 81 (4):751-6, 2005.	In systematic review
Gunther CW, Legowski PA, Lyle RM et al. Parathyroid hormone is associated with decreased fat mass in young healthy women. International Journal of Obesity 30 (1):94-9, 2006.	Ca intake and BW measured but not assessed ==> no relevant results reported
Haddad JG, Jr., Rojanasathit S. Acute administration of 25-hydroxycholecalciferol in man. Journal of Clinical Endocrinology & Metabolism 42 (2):284 -90, 1976.	Not RCT arrow 4 study
Hakala P, Karvetti RL. Weight reduction on lactovegetarian and mixed diets. Changes in weight, nutrient intake, skinfold thicknesses and blood pressure. European Journal of Clinical Nutrition 43 (6):421-30, 1989.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Halhali A, Villa AR, Madrazo E et al. Longitudinal changes in maternal serum 1,25-dihydroxyVitamin D and insulin like growth factor I levels in pregnant women who developed preeclampsia: comparison with normotensive pregnant women. Journal of Steroid Biochemistry & Molecular Biology 89 -90 (1-5):553-6, 2004.	No outcomes of interest
Hamet P, Mongeau E, Lambert J et al. Interactions among calcium, sodium, and alcohol intake as determinants of blood pressure. Hypertension 17(1 Suppl):I150-4, 1991.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Hamid Z, Riggs A, Spencer T, Redman C, Bodenner D. Vitamin D deficiency in residents of academic long-term care facilities despite having been prescribed Vitamin D.. Journal of the American Medical Directors Association 2007; 8(2):71-75.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Hansen KE, Jones AN, Lindstrom MJ, Davis LA, Engelke JA, Shafer MM. Vitamin D insufficiency: disease or no disease? Journal of Bone & Mineral Research 23(7):1052-60, 2008.	Not RCT arrow 4 study
Haub MD, Simons TR, Cook CM, Remig VM, Al-Tamimi EK, Holcomb CA. Calcium-fortified beverage supplementation on body composition in postmenopausal women. Nutrition Journal 4:21, 2005.	In systematic review
Heilbrun LK, Hankin JH, Nomura AM, Stemmermann GN. Colon cancer and dietary fat, phosphorus, and calcium in Hawaiian-Japanese men. American Journal of Clinical Nutrition 43 (2):306-9, 1986.	Letter to the editor
Heilbrun LK, Nomura A, Hankin JH, Stemmermann GN. Dietary Vitamin D and calcium and risk of colorectal cancer. Lancet 1985; 1(8434):925.	Superceded by Stemmermann, 1990 RefID 1691
Herrera JA, revalo-Herrera M, Herrera S. Prevention of preeclampsia by linoleic acid and calcium supplementation: a randomized controlled trial. Obstetrics & Gynecology 91 (4):585 -90, 1998.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect

Excluded Study	Reason
Herrmann U, Schwille PO, Schmiedl A, Fan J, Manoharan M. Acute effects of calcium sodium citrate supplementation of a test meal on mineral homeostasis, oxalate, and calcium oxalate crystallization in the urine of healthy humans--preliminary results in patients with idiopathic calcium urolithiasis. Biomedicine & Pharmacotherapy 53 (5-6):264-73, 1999.	No UL outcomes: CaOx crystallization; saturation of CaOx
Hill KM, Braun M, Kern M et al. Predictors of calcium retention in adolescent boys. Journal of Clinical Endocrinology & Metabolism 93 (12):4743 -8, 2008.	no outcomes of interest
Hiller JE, Crowther CA, Moore VA, Willson K, Robinson JS. Calcium supplementation in pregnancy and its impact on blood pressure in children and women: follow up of a randomised controlled trial. Australian & New Zealand Journal of Obstetrics & Gynaecology 2007; 47(2):115-121.	No outcomes of interest
Hillman LS, Haddad JG. Perinatal Vitamin D metabolism. II. Serial 25-hydroxyVitamin D concentrations in sera of term and premature infants. Journal of Pediatrics 1975; 86(6):928-935.	No clear Vitamin D dose for term infants
Hillman LS, Johnson LS, Lee DZ, Vieira NE, Yergey AL. Measurement of true absorption, endogenous fecal excretion, urinary excretion, and retention of calcium in term infants by using a dual-tracer, stable-isotope method. Journal of Pediatrics 1993; 123(3):444-456.	All neonates included weighed < 1500 gm
Hintzpeter B, Mensink GB, Thierfelder W, Muller MJ, Scheidt-Nave C. Vitamin D status and health correlates among German adults. European Journal of Clinical Nutrition 62 (9):1079 -89, 2008.	cross-sectional or retrospective assessment of diet after disease diagnosis
Hofmeyr GJ, Mlokoti Z, Nikodem VC et al. Calcium supplementation during pregnancy for preventing hypertensive disorders is not associated with changes in platelet count, urate, and urinary protein: a randomized control trial. Hypertension in Pregnancy 27 (3):299 -304, 2008.	ancillary study (small sample) of WHO trial. The preeclampsia data of WHO trial was already included in the previous SR (Hofmeyer2007).
Hofstad B, Almendingen K, Vatn M et al. Growth and recurrence of colorectal polyps: a double-blind 3-year intervention with calcium and antioxidants. Digestion 59 (2):148-56, 1998.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Hofstad B, Vatn MH, Andersen SN, Owen RW, Larsen S, Osnes M. The relationship between faecal bile acid profile with or without supplementation with calcium and antioxidants on recurrence and growth of colorectal polyps. European Journal of Cancer Prevention 7 (4):287-94, 1998.	No independent Ca effect
Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypoVitaminosis D for both the mother and the nursing infant. Am J Clin Nutr 2004; 80(6 Suppl):1752S-1758S.	In Ottawa EPC report
Hollis JH, Mattes RD. Effect of increased dairy consumption on appetitive ratings and food intake. [erratum appears in Obesity (Silver Spring). 2007 Oct;15(10):2520]. Obesity 2007; 15(6):1520-1526.	No outcomes of interest
Holt PR, Atillasoy EO, Gilman J et al. Modulation of abnormal colonic epithelial cell proliferation and differentiation by low-fat dairy foods: a randomized controlled trial. JAMA 280 (12):1074-9, 1998.	No outcomes of interest
Holt PR, Bresalier RS, Ma CK et al. Calcium plus Vitamin D alters preneoplastic features of colorectal adenomas and rectal mucosa. Cancer 106 (2):287-96, 2006.	No outcomes of interest
Holt PR, Wolper C, Moss SF, Yang K, Lipkin M. Comparison of calcium supplementation or low-fat dairy foods on epithelial cell proliferation and differentiation. Nutrition & Cancer 41 (1-2):150-5, 2001.	No outcomes of interest
Hunt CD, Johnson LK. Calcium requirements: new estimations for men and women by cross-sectional statistical analyses of calcium balance data from metabolic studies. American Journal of Clinical Nutrition 2007; 86(4):1054-1063.	Arrow 4: calcium balance
Hvarfner A, Ljunghall S, Morlin C, Wide L. Calcium metabolism and arterial blood pressure in a healthy population sample and in hypertensive men. American Journal of Nephrology 6 Suppl 1:14-5, 1986.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Hyman J, Baron JA, Dain BJ et al. Dietary and supplemental calcium and the recurrence of colorectal adenomas. Cancer Epidemiology, Biomarkers & Prevention 7 (4):291-5, 1998.	Multiple antioxidant trials analyses
Hypponen E, Hartikainen AL, Sovio U, Jarvelin MR, Pouta A. Does Vitamin D supplementation in infancy reduce the risk of pre-eclampsia? European Journal of Clinical Nutrition 2007; 61(9):1136-1139.	Observational study estimated Vitamin D supplement doses

Excluded Study	Reason
Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM. Intake of Vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 358 (9292):1500-3, 2001.	Observational study estimated Vitamin D supplement doses
Hypponen E, Sovio U, Wjst M et al. Infant Vitamin d supplementation and allergic conditions in adulthood: northern Finland birth cohort 1966. Annals of the New York Academy of Sciences 1037:84-95, 2004.	Observational study estimated Vitamin D supplement doses
Ilich-Ernst JZ, McKenna AA, Badenhop NE et al. Iron status, menarche, and calcium supplementation in adolescent girls.[erratum appears in Am J Clin Nutr 1999 Mar;69(3):577]. American Journal of Clinical Nutrition 68 (4):880-7, 1998.	Ca intake, BMI, LBM and BW measured, but the analyses on the relationship among these were not performed.
Ish-Shalom S, Segal E, Salganik T, Raz B, Bromberg IL, Vieth R. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. Journal of Clinical Endocrinology & Metabolism 93 (9):3430 -5, 2008.	arrow 4 RCT but daily doses were the same in the comparison groups (comparison of daily, weekly versus monthly dose)
Ito M, Koyama H, Ohshige A, Maeda T, Yoshimura T, Okamura H. Prevention of preeclampsia with calcium supplementation and Vitamin D3 in an antenatal protocol. International Journal of Gynaecology & Obstetrics 47 (2):115 -20, 1994.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Jackson RD, Donepudi S, Mysiw WJ. Epidemiology of fracture risk in the Women's Health Initiative. Current Osteoporosis Reports 6 (4):155 -61, 2008.	review paper
Jackson RD, Lacroix AZ, Cauley JA, McGowan J. The Women's Health Initiative calcium-Vitamin D trial: overview and baseline characteristics of participants. Annals of Epidemiology 13(9 Suppl):S98-106, 2003.	Overview of trial participants
Jackson RD, Lacroix AZ, Gass M et al. Calcium plus Vitamin D supplementation and the risk of fractures.[erratum appears in N Engl J Med. 2006 Mar 9;354(10):1102]. New England Journal of Medicine 354 (7):669-83, 2006.	Same as Wactawski-Wende 2006 RefID 1967 in which longer f/up data reported
Jacobs D. Calcium and myocardial infarction. South African Medical Journal Suid -Afrikaanse Tydskrif Vir Geneeskunde 48 (13):523-7, 1974.	No 25(OH)D or dietary Ca
Jacobs ET, Alberts DS, Benuzillo J, Hollis BW, Thompson PA, Martinez ME. Serum 25(OH)D levels, dietary intake of Vitamin D, and colorectal adenoma recurrence. Journal of Steroid Biochemistry & Molecular Biology 2007; 103(3-5):752-756.	Analyses include 25(OH)D measurements taken after outcome (colorectal polyps) occurred.
Jacques PF, Felson DT, Tucker KL et al. Plasma 25-hydroxyVitamin D and its determinants in an elderly population sample. American Journal of Clinical Nutrition 66 (4):929-36, 1997.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Joffe GM, Esterlitz JR, Levine RJ et al. The relationship between abnormal glucose tolerance and hypertensive disorders of pregnancy in healthy nulliparous women. Calcium for Preeclampsia Prevention (CPEP) Study Group.. American Journal of Obstetrics & Gynecology 179 (4):1032-7, 1998.	No 25(OH)D or dietary Ca
John EM, Dreon DM, Koo J, Schwartz GG. Residential sunlight exposure is associated with a decreased risk of prostate cancer. Journal of Steroid Biochemistry & Molecular Biology 89 -90 (1-5):549 -52, 2004.	No 25(OH)D or dietary Ca
John WG, Noonan K, Mannan N, Boucher BJ. HypoVitaminosis D is associated with reductions in serum apolipoprotein A-I but not with fasting lipids in British Bangladeshis. American Journal of Clinical Nutrition 82 (3):517-22, 2005.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Johnson MA, Fischer JG, Park S. Vitamin D deficiency and insufficiency in the Georgia Older Americans Nutrition Program. Journal of Nutrition for the Elderly 27 (1-2):29 -46, 2008.	combination of vit D/Ca and other treatment w/o analysis of independent effect
Johnson NE, Smith EL, Freudenheim JL. Effects on blood pressure of calcium supplementation of women. American Journal of Clinical Nutrition 42 (1):12-7, 1985.	In systematic review
Jones G, Scott F. Low bone mass in premenopausal parous women: identification and the effect of an information and bone density feedback program. Journal of Clinical Densitometry 2(2):109-15, 1999.	No outcomes of interest
Jorde R, Bonaa KH. Calcium from dairy products, Vitamin D intake, and blood pressure: the Tromso Study.. American Journal of Clinical Nutrition 71 (6):1530-5, 2000.	No outcomes of interest
Kampman E, Giovannucci E, van ', V et al. Calcium, Vitamin D, dairy foods, and the occurrence of colorectal adenomas among men and women in two prospective studies. Am J Epidemiol 1994; 139(1):16-29.	Same cohorts as Wu 2002 RefID 529 (HPFS & NHS) and same exposure-outcome relationship but shorter follow-up

Excluded Study	Reason
Karanja N, Morris CD, Illingworth DR, McCarron DA. Plasma lipids and hypertension: response to calcium supplementation. American Journal of Clinical Nutrition 45 (1):60-5, 1987.	No outcomes of interest
Karanja N, Morris CD, Rufolo P, Snyder G, Illingworth DR, McCarron DA. Impact of increasing calcium in the diet on nutrient consumption, plasma lipids, and lipoproteins in humans. American Journal of Clinical Nutrition 59 (4):900-7, 1994.	No outcomes of interest
Kawano Y. Role of blood pressure monitoring in non-pharmacological management of hypertension. Blood Pressure Monitoring 7 (1):51-4, 2002.	Review paper
Kearney J, Giovannucci E, Rimm EB et al. Calcium, Vitamin D, and dairy foods and the occurrence of colon cancer in men. American Journal of Epidemiology 143 (9):907-17, 1996.	Longer followup data were published in Wu 2002
Kemi VE, Karkkainen MU, Karp HJ, Laitinen KA, Lamberg-Allardt CJ. Increased calcium intake does not completely counteract the effects of increased phosphorus intake on bone: an acute dose-response study in healthy females. British Journal of Nutrition 99 (4):832-9, 2008.	No outcomes of interest
Kenny AM, Bellantonio S, Gruman CA, Acosta RD, Prestwood KM. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 57 (5):M321-5, 2002.	No 25(OH)D or dietary Ca
Kenny AM, Biskup B, Robbins B, Marcella G, Burleson JA. Effects of Vitamin D supplementation on strength, physical function, and health perception in older, community-dwelling men. Journal of the American Geriatrics Society 51 (12):1762-7, 2003.	In Ottawa EPC report
Kesteloot H, Geboers J. Calcium and blood pressure. Lancet 1(8276):813 -5, 1982.	No 25(OH)D or dietary Ca
Khaw KT, Barrett-Connor E. Dietary potassium and stroke-associated mortality. A 12-year prospective population study. New England Journal of Medicine 316 (5):235-40, 1987.	Continuous Ca intake analysis only
Kigutha HN, van Staveren WA, Wijnhoven TM, Hautvast JG. Maternal nutritional status may be stressed by seasonal fluctuations in food availability: evidence from rural women in Kenya. International Journal of Food Sciences & Nutrition 46 (3):247-55, 1995.	Ca intake, BMI and BW measured, but analysis did not relate Ca intake to BMI/BW.
Knekt P, Laaksonen M, Mattila C et al. Serum Vitamin D and subsequent occurrence of type 2 diabetes. Epidemiology. 19(5):666-71, 2008 Sep.	No outcomes of interest
Knight KB, Keith RE. Calcium supplementation on normotensive and hypertensive pregnant women. American Journal of Clinical Nutrition 55 (4):891-5, 1992.	No outcomes of interest
Knox EG. Ischaemic-heart-disease mortality and dietary intake of calcium. Lancet 1(7818):1465-7, 1973.	Analysis @ region level, not individual level
Kobayashi E, Okubo Y, Suwazono Y et al. Association between urinary calcium excretion level and mortality in inhabitants of the Jinzu River basin area of Japan. Biological Trace Element Research 89(2):145-53, 2002.	No 25(OH)D or dietary Ca
Koh-Banerjee PK, Ferreira MP, Greenwood M et al. Effects of calcium pyruvate supplementation during training on body composition, exercise capacity, and metabolic responses to exercise. Nutrition 21(3):312-9, 2005.	No 25(OH)D or dietary Ca
Kokot F, Pietrek J, Srokowska S et al. 25-hydroxyVitamin D in patients with essential hypertension. Clinical Nephrology 16 (4):188-92, 1981.	On drug Rx for hypertension
Koralek DO, Bertone-Johnson ER, Leitzmann MF et al. Relationship between calcium, lactose, Vitamin D, and dairy products and ovarian cancer. Nutrition & Cancer 2006; 56(1):22-30.	No outcomes of interest
Kristal AR, Chi C, Tangen CM, Goodman PJ, Etzioni R, Thompson IM. Associations of demographic and lifestyle characteristics with prostate-specific antigen (PSA) concentration and rate of PSA increase. Cancer 106 (2):320-8, 2006.	No outcomes of interest
Kromhout D, Bosschieter EB, Coulander CD. Potassium, calcium, alcohol intake and blood pressure: the Zutphen Study. American Journal of Clinical Nutrition 41 (6):1299-304, 1985.	No outcomes of interest
Kulier R, de OM, Gulmezoglu AM, Villar J. Nutritional interventions for the prevention of maternal morbidity. International Journal of Gynaecology & Obstetrics 63 (3):231-46, 1998.	SR of prevention of maternal morbidity

Excluded Study	Reason
Kumar R, Cohen WR, Silva P, Epstein FH. Elevated 1,25-dihydroxyVitamin D plasma levels in normal human pregnancy and lactation. Journal of Clinical Investigation 63 (2):342-4, 1979.	No outcomes of interest
Kuroda T, Shiraki M, Tanaka S, Ohta H. Contributions of 25-hydroxyvitamin D, co-morbidities and bone mass to mortality in Japanese postmenopausal women. Bone 44 (1):168 -72, 2009.	>=20% subjects with diseases
Kynast-Gales SA, Massey LK. Effects of dietary calcium from dairy products on ambulatory blood pressure in hypertensive men.. Journal of the American Dietetic Association 92 (12):1497-501, 1992.	In systematic review
Laaksi I, Ruohola JP, Tuohimaa P et al. An association of serum Vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. American Journal of Clinical Nutrition 86 (3):714-7, 2007.	No outcomes of interest
Lakdawala DR, Widdowson EM. Vitamin-D in human milk. Lancet 1(8004):167-8, 1977.	No outcomes of interest
Lamberg-Allardt C, Larjosto M, Schultz E. 25-HydroxyVitamin D concentrations in maternal and cord blood at delivery and in maternal blood during lactation in Finland. Human Nutrition - Clinical Nutrition 38 (4):261-8, 1984.	Not RCT arrow 4 study
Lancia B, Tedesco M, Sergio G, Tenna M. Anthropometric and nutritional assessment in Italian elderly subjects. Journal of Nutrition, Health & Aging 1(3):174-80, 1997.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Lappe JM, Davies KM, Travers-Gustafson D, Heaney RP. Vitamin D status in a rural postmenopausal female population. Journal of the American College of Nutrition 2006; 25(5):395-402.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Laraia BA, Bodnar LM, Siega-Riz AM. Pregravid body mass index is negatively associated with diet quality during pregnancy. Public Health Nutrition 2007; 10(9):920-926.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Lasco A, Gaudio A, Morini E et al. Effect of long-term treatment with raloxifene on mammary density in postmenopausal women. Menopause 2006; 13(5):787-792.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Latham NK, Anderson CS, Lee A et al. A randomized, controlled trial of quadriceps resistance exercise and Vitamin D in frail older people: the Frailty Interventions Trial in Elderly Subjects (FITNESS). Journal of the American Geriatrics Society 51 (3):291-9, 2003.	In Ottawa EPC report
Le BN, Cancela L, Miravet L. Calcidiol in human milk. The effect of prohormone on Vitamin D status of breast fed unsupplemented infants. Endocrinologia Experimentalis. 20(2-3):325-8, 1986.	Correlation b/tw breastmilk 25(OH)D with infant's serum 25(OH)D
Lee DC, Lee GY. The use of pamidronate for hypercalcemia secondary to acute Vitamin D intoxication. Journal of Toxicology - Clinical Toxicology 36 (7):719-21, 1998.	Case report
Lee WT, Leung SS, Wang SH et al. Double-blind, controlled calcium supplementation and bone mineral accretion in children accustomed to a low-calcium diet.. American Journal of Clinical Nutrition 60 (5):744 -50, 1994.	In Winzenberg 2007 systematic review, no outcomes of interest
Levine AJ, Harper JM, Ervin CM et al. Serum 25-hydroxyVitamin D, dietary calcium intake, and distal colorectal adenoma risk. Nutrition & Cancer 2001; 39(1):35-41.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Levine RJ, Esterlitz JR, Raymond EG et al. Trial of Calcium for Preeclampsia Prevention (CPEP): rationale, design, and methods. Controlled Clinical Trials 17(5):442-69, 1996.	Methods for trial
Levine RJ, Hauth JC, Curet LB et al. Trial of calcium to prevent preeclampsia.. New England Journal of Medicine 337 (2):69-76, 1997.	In Hofmeyer 2007 systematic review
Lewandowski S, Rodgers AL. Renal response to lithogenic and anti-lithogenic supplement challenges in a stone-free population group. Journal of Renal Nutrition 14(3):170-9, 2004.	No UL outcomes: saturation of CaOx
Liebman M, Chopin LF, Carter E et al. Factors related to blood pressure in a biracial adolescent female population. Hypertension 8(10):843-50, 1986.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Lin PH, Appel LJ, Funk K et al. The PREMIER intervention helps participants follow the Dietary Approaches to Stop Hypertension dietary pattern and the current Dietary Reference Intakes recommendations. Journal of the American Dietetic Association 2007; 107(9):1541-1551.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect

Excluded Study	Reason
Lin YC, Lyle RM, McCabe LD, McCabe GP, Weaver CM, Teegarden D. Dairy calcium is related to changes in body composition during a two-year exercise intervention in young women. Journal of the American College of Nutrition. 19(6):754-60, 2000 Nov-Dec.	No outcomes of interest
Lind L, Lithell H, Skarfors E, Wide L, Ljunghall S. Reduction of blood pressure by treatment with alphacalcidol. A double-blind, placebo-controlled study in subjects with impaired glucose tolerance. Acta Medica Scandinavica 223 (3):211-7, 1988.	>=20% subjects with diseases
Lipkin M, Friedman E, Winawer SJ, Newmark H. Colonic epithelial cell proliferation in responders and nonresponders to supplemental dietary calcium. Cancer Research 49 (1):248 -54, 1989.	>=20% subjects with diseases
Lipkin M, Newmark H. Effect of added dietary calcium on colonic epithelial-cell proliferation in subjects at high risk for familial colonic cancer. New England Journal of Medicine 313 (22):1381-4, 1985.	No outcomes of interest
Liu LS. Epidemiology of hypertension and cardiovascular disease--China experience. Clinical & Experimental Hypertension - Part A, Theory & Practice 12 (5):831-44, 1990.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Liu S, Choi HK, Ford E et al. A prospective study of dairy intake and the risk of type 2 diabetes in women. Diabetes Care 29 (7):1579-84, 2006.	No 25(OH)D or dietary Ca
Ljunghall S, Lind L, Lithell H et al. Treatment with one-alpha-hydroxycholecalciferol in middle-aged men with impaired glucose tolerance--a prospective randomized double-blind study. Acta Medica Scandinavica 222 (4):361-7, 1987.	>=20% subjects with diseases
Lonzer MD, Imrie R, Rogers D, Worley D, Licata A, Secic M. Effects of heredity, age, weight, puberty, actiVitaminy, and calcium intake on bone mineral density in children. Clinical Pediatrics 35 (4):185-9, 1996.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Lopez-Jaramillo P, Delgado F, Jacome P, Teran E, Ruano C, Rivera J. Calcium supplementation and the risk of preeclampsia in Ecuadorian pregnant teenagers. Obstetrics & Gynecology 90 (2):162-7, 1997.	In Hofmeyer 2007 systematic review
Lopez-Jaramillo P, Narvaez M, Weigel RM, Yepez R. Calcium supplementation reduces the risk of pregnancy-induced hypertension in an Andes population. British Journal of Obstetrics & Gynaecology 96 (6):648 -55, 1989.	In Hofmeyer 2007 systematic review
Luft FC, Aronoff GR, Sloan RS, Fineberg NS, Weinberger MH. Short-term augmented calcium intake has no effect on sodium homeostasis. Clinical Pharmacology & Therapeutics 39 (4):414-9, 1986.	No outcomes of interest
Lutter CK, Rodriguez A, Fuenmayor G, Avila L, Sempertegui F, Escobar J. Growth and micronutrient status in children receiving a fortified complementary food. Journal of Nutrition 138 (2):379-88, 2008.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Lyle RM. Does baseline serum total calcium level influence the blood pressure response to calcium supplementation? A double-blind study. Netherlands Journal of Medicine 41 (1-2):48-55, 1992.	In systematic review
Lynch MF, Griffin IJ, Hawthorne KM, Chen Z, Hamzo M, Abrams SA. Calcium balance in 1-4-y-old children. American Journal of Clinical Nutrition 2007; 85(3):750-754.	Arrow 4: calcium balance
Ma J, Stampfer MJ, Gann PH et al. Vitamin D receptor polymorphisms, circulating Vitamin D metabolites, and risk of prostate cancer in United States physicians. Cancer Epidemiology, Biomarkers & Prevention 7 (5):385-90, 1998.	Main results had been previous published (Gann 1996, RefID 3783), and no additional usable data
Macdonald HM, New SA, Campbell MK, Reid DM. Longitudinal changes in weight in perimenopausal and early postmenopausal women: effects of dietary energy intake, energy expenditure, dietary calcium intake and hormone replacement therapy. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity 27 (6):669-76, 2003.	No outcomes of interest
Madore F, Stampfer MJ, Rimm EB, Curhan GC. Nephrolithiasis and risk of hypertension. American Journal of Hypertension 11(1 Pt 1):46-53, 1998.	No outcomes of interest
Malila N, Virtanen M, Pietinen P et al. A comparison of prospective and retrospective assessments of diet in a study of colorectal cancer. Nutrition & Cancer 32 (3):146 -53, 1998.	Superseded by Pietinen 1999

Excluded Study	Reason
Mandic-Puljek M, Mandic ML, Perl A, Kenjeric D. Calcium intake, food sources and seasonal variations in eastern Croatia. Collegium Antropologicum 29 (2):503-7, 2005.	No outcomes of interest
Manios Y, Moschonis G, Grammatikaki E, Katsaroli I, Kanelou P, Tanagra S. Nutrition education in postmenopausal women: changes in dietary and cardiovascular indices. Maturitas 2006; 55(4):338-347.	Nutrition education intervention study
Marangella M, Vitaminale C, Petrarulo M, Rovera L, Dutto F. Effects of mineral composition of drinking water on risk for stone formation and bone metabolism in idiopathic calcium nephrolithiasis. Clinical Science 91 (3):313-8, 1996.	No UL outcomes: saturation of CaOx
Markestad T, Kolmannskog S, Arntzen E, Toftegaard L, Haneberg B, Aksnes L. Serum concentrations of Vitamin D metabolites in exclusively breast-fed infants at 70 degrees north. Acta Paediatrica Scandinavica 73 (1):29-32, 1984.	No relation with 25(OH)D to growth outcome
Markestad T. Effect of season and Vitamin D supplementation on plasma concentrations of 25-hydroxyVitamin D in Norwegian infants. Acta Paediatrica Scandinavica 72 (6):817-21, 1983.	Not RCT arrow 4 study
Markestad T. Plasma concentrations of Vitamin D metabolites in unsupplemented breast-fed infants. European Journal of Pediatrics 141 (2):77-80, 1983.	No outcomes of interest
Marniemi J, Jarvisalo J, Toikka T, Raiha I, Ahotupa M, Sourander L. Blood Vitamins, mineral elements and inflammation markers as risk factors of vascular and non-vascular disease mortality in an elderly population. International Journal of Epidemiology 27 (5):799-807, 1998.	No 25(OH)D or dietary Ca
Martinez ME, Giovannucci EL, Colditz GA et al. Calcium, Vitamin D, and the occurrence of colorectal cancer among women. Journal of the National Cancer Institute 88 (19):1375-82, 1996.	Longer followup data were published in Wu 2002
Marx SJ, Swart EG, Jr., Hamstra AJ, DeLuca HF. Normal intrauterine development of the fetus of a woman receiving extraordinarily high doses of 1,25-dihydroxyVitamin D3. Journal of Clinical Endocrinology & Metabolism 51 (5):1138 -42, 1980.	Case report
Masse PG, Tranchant CC, Jougleux JL, Coburn SP, Cole DE. Cardiovascular disease-risk factors in middle-aged osteopaenic women treated with calcium alone or combined to three nutrients essential to artery and bone collagen. Journal of Human Nutrition & Dietetics 21(2):117-28, 2008.	No outcomes of interest
Matheson NA. Letter: Multiple sclerosis and diet. Lancet 2 (7884):831, 1974.	Letter to the editor
Matsumoto T, Kubodera N. ED-71, a new active Vitamin D3, increases bone mineral density regardless of serum 25(OH)D levels in osteoporotic subjects. Journal of Steroid Biochemistry & Molecular Biology 2007; 103(3-5):584-586.	Vitamin D analog
Mawer EB, Berry JL, Sommer-Tsilenis E, Beykirch W, Kuhlwein A, Rohde BT. Ultraviolet irradiation increases serum 1,25-dihydroxyVitamin D in Vitamin-D-replete adults. Mineral & Electrolyte Metabolism 10(2):117-21, 1984.	Not RCT arrow 4 study
Mazess RB, Peppler WW, Chesnut CH, III, Nelp WB, Cohn SH, Zanzi I. Total body bone mineral and lean body mass by dual-photon absorptiometry. II. Comparison with total body calcium by neutron activation analysis. Calcified Tissue International 33 (4):361-3, 1981.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Mazess RB, Peppler WW, Harrison JE, McNeill KG. Total body bone mineral and lean body mass by dual-photon absorptiometry. III. Comparison with trunk calcium by neutron activation analysis. Calcified Tissue International 33 (4):365-8, 1981.	No 25(OH)D or dietary Ca
McCarron DA, Morris CD. Blood pressure response to oral calcium in persons with mild to moderate hypertension. A randomized, double-blind, placebo-controlled, crossover trial. Annals of Internal Medicine 103 (6 (Pt 1)):825 -31, 1985.	In systematic review
Merlino LA, Curtis J, Mikuls TR et al. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study.. Arthritis & Rheumatism 50(1):72-7, 2004.	Observational study estimated Vitamin D supplement doses
Methy N, Binquet C, Boutron-Ruault MC, Paillot B, Faivre J, Bonithon-Kopp C. Dietary fatty acids and recurrence of colorectal adenomas in a European intervention trial. Nutrition & Cancer 60 (5):560-7, 2008.	no 25(OH)D or dietary Ca

Excluded Study	Reason
Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Willett WC, Giovannucci E. Prospective study of dietary supplements, macronutrients, micronutrients, and risk of bladder cancer in US men. American Journal of Epidemiology 152 (12):1145-53, 2000.	No outcomes of interest
Misselwitz J, Hesse V, Markestad T. Nephrocalcinosis, hypercalciuria and elevated serum levels of 1,25-dihydroxyVitamin D in children. Possible link to Vitamin D toxicity. Acta Paediatrica Scandinavica 79 (6-7):637-43, 1990.	Case report
Moerman CJ, Smeets FW, Kromhout D. Dietary risk factors for clinically diagnosed gallstones in middle-aged men. A 25-year follow-up study (the Zutphen Study). Annals of Epidemiology 4(3):248-54, 1994.	No outcomes of interest
Mohr SB, Garland CF, Gorham ED, Garland FC. The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. Diabetologia 51 (8):1391-8, 2008.	ecological study
Moller UK, Ramlau-Hansen CH, Rejnmark L, Heickendorff L, Henriksen TB, Mosekilde L. Postpartum Vitamin D insufficiency and secondary hyperparathyroidism in healthy Danish women. European Journal of Clinical Nutrition 2006; 60(10):1214-1221.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Morley R, Carlin JB, Dwyer T. Maternal calcium supplementation and cardiovascular risk factors in twin offspring. International Journal of Epidemiology 33 (6):1304-9, 2004.	No 25(OH)D or dietary Ca
Morosetti M, Jankovic L, Palombo G et al. High-dose calcitriol therapy and progression of cardiac vascular calcifications. Journal of Nephrology 21(4):603 - 8, 2008; Aug.	i.v. calcitriol
Morris CD, McCarron DA. Effect of calcium supplementation in an older population with mildly increased blood pressure. American Journal of Hypertension 5(4 Pt 1):230-7, 1992.	No outcomes of interest
Munger KL, Levin LI, Hollis BW, Howard NS, Ascherio A. Serum 25-hydroxyVitamin D levels and risk of multiple sclerosis. JAMA. 296(23):2832-8, 2006 Dec 20.	No outcomes of interest
Muray S, Marco MP, Craver L, Rue M, Valdivielso JM, Fernandez E. Influence of mineral metabolism parameters on pulse pressure in healthy subjects.. Clinical Nephrology 2006; 66(6):411-417.	No 25(OH)D or dietary Ca
Nakamura K, Nishiwaki T, Ueno K, Yamamoto M. Age-related decrease in serum 25-hydroxyVitamin D concentrations in the frail elderly: a longitudinal study. Journal of Bone & Mineral Metabolism 2007; 25(4):232-236.	Effect of aging on 25(OH) D
Nakamura R, Saruta T. Effect of calcium supplementation on blood pressure in essential hypertensive subjects. Japanese Journal of Medicine 26 (2):203-6, 1987.	No outcomes of interest
Nako Y, Fukushima N, Tomomasa T, Nagashima K, Kuroume T. HyperVitaminosis D after prolonged feeding with a premature formula. Pediatrics 1993; 92(6):862-864.	Case report
Narang NK, Gupta RC, Jain MK. Role of Vitamin D in pulmonary tuberculosis. Journal of the Association of Physicians of India 32 (2):185-8, 1984.	No outcomes of interest
Nayir A, Kadioglu A, Sirin A, Emre S, Tonguc E, Bilge I. Causes of increased renal medullary echogenicity in Turkish children. Pediatric Nephrology 9 (6):729-33, 1995.	Case report
Need AG, O'Loughlin PD, Horowitz M, Nordin BE. Relationship between fasting serum glucose, age, body mass index and serum 25 hydroxyVitamin D in postmenopausal women. Clinical Endocrinology 62 (6):738-41, 2005.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Nieves JW, Barrett-Connor E, Siris ES, Zion M, Barlas S, Chen YT. Calcium and vitamin D intake influence bone mass, but not short-term fracture risk, in Caucasian postmenopausal women from the National Osteoporosis Risk Assessment (NORA) study. Osteoporosis International 1919;673-9.	not RCT bone study (postmenopausal women)
Nilas L, Christiansen C. Treatment with Vitamin D or its analogues does not change body weight or blood glucose level in postmenopausal women. International Journal of Obesity 8(5):407-11, 1984.	Review paper
Niromanesh S, Laghaii S, Mosavi-Jarrahi A. Supplementary calcium in prevention of pre-eclampsia. International Journal of Gynaecology & Obstetrics 74 (1):17-21, 2001.	In Hofmeyer 2007 systematic review

Excluded Study	Reason
Nishimura K, Shima M, Tsugawa N et al. Long-term hospitalization during pregnancy is a risk factor for Vitamin D deficiency in neonates.[erratum appears in J Bone Miner Metab. 2003;21(4):253]. Journal of Bone & Mineral Metabolism 21(2):103-8, 2003.	No outcomes of interest
Nishiyama T. Effects of calcium on muscular training. Journal of Nutritional Science & Vitaminology 31 Suppl: S45-7, 1985.	Calcium only and bone/muscle outcomes
Nowak A, Pachocka L, Targosz U, Klosiewicz-Latoszek L. Dietary calcium and obesity in men. Roczniki Panstwowego Zakladu Higieny 58 (1):301-5, 2007.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Nowson C, Morgan T. Effect of calcium carbonate on blood pressure in normotensive and hypertensive people. Hypertension 13(6 Pt 1):630-9, 1989.	In systematic review
Obarzanek E, Hunsberger SA, Van HL et al. Safety of a fat-reduced diet: the Dietary Intervention Study in Children (DISC). Pediatrics 100 (1):51-9, 1997.	No outcomes of interest
Ochner CN, Lowe MR. Self-reported changes in dietary calcium and energy intake predict weight regain following a weight loss diet in obese women. Journal of Nutrition 2007; 137(10):2324-2328.	No outcomes of interest
Olafsdottir AS, Wagner KH, Thorsdottir I, Elmadfa I. Fat-soluble Vitamins in the maternal diet, influence of cod liver oil supplementation and impact of the maternal diet on human milk composition. Annals of Nutrition & Metabolism 45 (6):265-72, 2001.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Paganus A, Juntunen-Backman K, Savilahti E. Follow-up of nutritional status and dietary survey in children with cow's milk allergy. Acta Paediatrica 81 (6-7):518 -21, 1992.	>=20% subjects with diseases
Palacios C, Benedetti P, Fonseca S. Impact of calcium intake on body mass index in Venezuelan adolescents. Puerto Rico Health Sciences Journal 26 (3):199-204, 2007.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Park SB, Suh DH, Youn JI. A pilot study to assess the safety and efficacy of topical calcipotriol treatment in childhood psoriasis. Pediatric Dermatology 16 (4):321-5, 1999.	No 25(OH)D or dietary Ca
Pasch A, Frey FJ, Eisenberger U, Mohaupt MG, Bonny O. PTH and 1.25 vitamin D response to a low-calcium diet is associated with bone mineral density in renal stone formers. Nephrology Dialysis Transplantation 23(8):2563-70, 2008.	no outcomes of interest
Pehlivan I, Hatun S, Aydogan M, Babaoglu K, Gokalp AS. Maternal Vitamin D deficiency and Vitamin D supplementation in healthy infants. Turkish Journal of Pediatrics 45 (4):315-20, 2003;-Dec.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Peters U, Hayes RB, Chatterjee N et al. Circulating Vitamin D metabolites, polymorphism in Vitamin D receptor, and colorectal adenoma risk. Cancer Epidemiology, Biomarkers & Prevention 2004; 13(4):546-552.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Peters U, McGlynn KA, Chatterjee N et al. Vitamin D, calcium, and Vitamin D receptor polymorphism in colorectal adenomas. Cancer Epidemiology, Biomarkers & Prevention 2001; 10(12):1267-1274.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Pettifor JM, Bikle DD, Cavaleros M, Zachen D, Kamdar MC, Ross FP. Serum levels of free 1,25-dihydroxyVitamin D in Vitamin D toxicity. Annals of Internal Medicine 122 (7):511-3, 1995.	Case report
Phillips SM, Bandini LG, Cyr H, Colclough-Douglas S, Naumova E, Must A. Dairy food consumption and body weight and fatness studied longitudinally over the adolescent period. International Journal of Obesity & Related Metabolic Disorders: Journal of the International Association for the Study of Obesity 27 (9):1106-13, 2003.	Not RCT growth study
Pilz S, Dobnig H, Fischer JE et al. Low Vitamin d levels predict stroke in patients referred to coronary angiography. Stroke 39 (9):2611-3, 2008.	>=20% subjects with diseases
Pilz S, Dobnig H, Winklhofer-Roob B et al. Low serum levels of 25-hydroxyVitamin D predict fatal cancer in patients referred to coronary angiography. Cancer Epidemiology, Biomarkers & Prevention 17(5):1228-33, 2008.	>=20% subjects with diseases
Pittard WB, III, Geddes KM, Hulsey TC, Hollis BW. How much Vitamin D for neonates? American Journal of Diseases of Children 145 (10):1147-9, 1991.	Not RCT arrow 4 study
Pittard WB, III, Geddes KM, Sutherland SE, Miller MC, Hollis BW. Longitudinal changes in the bone mineral content of term and premature infants. American Journal of Diseases of Children 1990; 144(1):36-40.	Changes in 25(OH)D status of term and premature infants

Excluded Study	Reason
Pittas AG, Harris SS, Stark PC, wson-Hughes B. The effects of calcium and Vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults.. Diabetes Care 2007; 30(4):980-986.	No outcomes of interest
Porojnicu AC, Robsahm TE, Dahlback A et al. Seasonal and geographical variations in lung cancer prognosis in Norway. Does Vitamin D from the sun play a role? Lung Cancer 2007; 55(3):263-270.	Ecological study
Prentice A, Ginty F, Stear SJ, Jones SC, Laskey MA, Cole TJ. Calcium supplementation increases stature and bone mineral mass of 16- to 18-year-old boys. Journal of Clinical Endocrinology & Metabolism 90 (6):3153-61, 2005.	In Winzenberg 2007 systematic review
Prineas RJ, Folsom AR, Zhang ZM, Sellers TA, Potter J. Nutrition and other risk factors for renal cell carcinoma in postmenopausal women. Epidemiology 8 (1):31-6, 1997.	No outcomes of interest
Purwar M, Kulkarni H, Motghare V, Dhole S. Calcium supplementation and prevention of pregnancy induced hypertension. Journal of Obstetrics & Gynaecology Research 22 (5):425-30, 1996.	In Hofmeyer 2007 systematic review
Rajalakshmi R, Sail SS, Shah DG, Ambady SK. The effects of supplements varying in carotene and calcium content on the physical, biochemical and skeletal status of preschool children. British Journal of Nutrition 30 (1):77-86, 1973.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Rajpathak SN, Rimm EB, Rosner B, Willett WC, Hu FB. Calcium and dairy intakes in relation to long-term weight gain in US men. American Journal of Clinical Nutrition 83 (3):559-66, 2006.	No outcomes of interest
Rees GA, Doyle W, Srivastava A, Brooke ZM, Crawford MA, Costeloe KL. The nutrient intakes of mothers of low birth weight babies - a comparison of ethnic groups in East London, UK. Maternal & Child Nutrition 1(2):91-9, 2005.	No outcomes of interest
Repke JT, Villar J, Anderson C, Pareja G, Dubin N, Belizan JM. Biochemical changes associated with blood pressure reduction induced by calcium supplementation during pregnancy. American Journal of Obstetrics & Gynecology 160 (3):684-90, 1989.	In Hofmeyer 2007 systematic review
Repke JT, Villar J. Pregnancy-induced hypertension and low birth weight: the role of calcium. American Journal of Clinical Nutrition 1991; 54(1:Suppl): Suppl-241S.	Review paper
Resnick LM, Oparil S, Chait A et al. Factors affecting blood pressure responses to diet: the Vanguard study. American Journal of Hypertension 13(9):956-65, 2000.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Reunanen A, Knekt P, Marniemi J, Maki J, Maatela J, Aromaa A. Serum calcium, magnesium, copper and zinc and risk of cardiovascular death. European Journal of Clinical Nutrition 50 (7):431-7, 1996.	No 25(OH)D or dietary Ca
Rich GM, McCullough M, Olmedo A, Malarick C, Moore TJ. Blood pressure and renal blood flow responses to dietary calcium and sodium intake in humans. American Journal of Hypertension 4(11):642S-645S, 1991.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Roberts CC, Chan GM, Folland D, Rayburn C, Jackson R. Adequate bone mineralization in breast-fed infants. Journal of Pediatrics 99 (2):192-6, 1981.	In Ottawa EPC report
Robien K, Cutler GJ, Lazovich D. Vitamin D intake and breast cancer risk in postmenopausal women: the Iowa Women's Health Study. Cancer Causes & Control 2007; 18(7):775-782.	Observational study estimated Vitamin D supplement doses
Rogers MS, Fung HY, Hung CY. Calcium and low-dose aspirin prophylaxis in women at high risk of pregnancy-induced hypertension. Hypertension in Pregnancy 18 (2):165-72, 1999.	In Hofmeyer 2007 systematic review
Roongpisuthipong C, Kantawan R, Roongpisuthipong W. Reduction of adipose tissue and body weight: effect of water soluble calcium hydroxycitrate in Garcinia atroviridis on the short term treatment of obese women in Thailand. Asia Pacific Journal of Clinical Nutrition 2007; 16(1):25-29.	No 25(OH)D or dietary Ca
Rosell M, Hakansson NN, Wolk A. Association between dairy food consumption and weight change over 9 y in 19,352 perimenopausal women. American Journal of Clinical Nutrition 2006; 84(6):1481-1488.	Ca intake and BW measured but not assessed ==> no relevant results reported
Rothberg AD, Pettifor JM, Cohen DF, Sonnendecker EW, Ross FP. Maternal-infant Vitamin D relationships during breast-feeding. Journal of Pediatrics 101 (4):500-3, 1982.	In Ottawa EPC report

Excluded Study	Reason
Rourke KM, Brehm BJ, Cassell C, Sethuraman G. Effect of weight change on bone mass in female adolescents. Journal of the American Dietetic Association 103 (3):369-72, 2003.	No 25(OH)D or dietary Ca
Rozen P, Fireman Z, Fine N, Wax Y, Ron E. Oral calcium suppresses increased rectal epithelial proliferation of persons at risk of colorectal cancer. Gut 30(5):650-5, 1989.	No outcomes of interest
Rozen P, Lubin F, Papo N et al. Calcium supplements interact significantly with long-term diet while suppressing rectal epithelial proliferation of adenoma patients. Cancer 91 (4):833-40, 2001.	No outcomes of interest
Rumiris D, Purwosunu Y, Wibowo N, Farina A, Sekizawa A. Lower rate of preeclampsia after antioxidant supplementation in pregnant women with low antioxidant status. Hypertension in Pregnancy 2006; 25(3):241-253.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Rush D, Sloan NL, Leighton J et al. The National WIC Evaluation: evaluation of the Special Supplemental Food Program for Women, Infants, and Children. V. Longitudinal study of pregnant women. American Journal of Clinical Nutrition 48 (2 Suppl):439-83, 1988.	No exposure of interest
Saadi HF, Dawodu A, Afandi B et al. Effect of combined maternal and infant vitamin D supplementation on vitamin D status of exclusively breastfed infants. Maternal & Child Nutrition 5(1):25 -32, 2009.	arrow 4 RCT but daily doses were the same in the comparison groups (comparison of daily vs. monthly doses)
Sacks FM, Brown LE, Appel L, Borhani NO, Evans D, Whelton P. Combinations of potassium, calcium, and magnesium supplements in hypertension. Hypertension 26 (6 Pt 1):950-6, 1995.	Combinations of minerals
Sacks FM, Obarzanek E, Windhauser MM et al. Rationale and design of the Dietary Approaches to Stop Hypertension trial (DASH). A multicenter controlled-feeding study of dietary patterns to lower blood pressure. Annals of Epidemiology 5(2):108-18, 1995.	No outcomes of interest
Sacks FM, Willett WC, Smith A, Brown LE, Rosner B, Moore TJ. Effect on blood pressure of potassium, calcium, and magnesium in women with low habitual intake. Hypertension 31 (1):131-8, 1998.	In systematic review
Saito K, Sano H, Kawahara J, Yokoyama M. Calcium supplementation attenuates an enhanced platelet function in salt-loaded mildly hypertensive patients. Hypertension 26 (1):156-63, 1995.	Data too incomplete
Sakhaee K, Baker S, Zerwekh J, Poindexter J, Garcia-Hernandez PA, Pak CY. Limited risk of kidney stone formation during long-term calcium citrate supplementation in nonstone forming subjects. Journal of Urology 152 (2 Pt 1):324-7, 1994.	No UL outcomes
Sakhaee K, Poindexter JR, Griffith CS, Pak CY. Stone forming risk of calcium citrate supplementation in healthy postmenopausal women. Journal of Urology 172 (3):958-61, 2004.	No UL outcomes: saturation of CaOx
Salazar-Martinez E, Lazcano-Ponce E, Sanchez-Zamorano LM, Gonzalez-Lira G, Escudero-DE Los RP, Hernandez-Avila M. Dietary factors and endometrial cancer risk. Results of a case-control study in Mexico. International Journal of Gynecological Cancer 15 (5):938-45, 2005.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Sampath V, Havel PJ, King JC. Calcium supplementation does not alter lipid oxidation or lipolysis in overweight/obese women. Obesity 16 (11):2400-4, 2008.	not RCT wt study
Sanchez-Ramos L, Adair CD, Kaunitz AM, Briones DK, Del Valle GO, Delke I. Calcium supplementation in mild preeclampsia remote from term: a randomized double-blind clinical trial. Obstetrics & Gynecology 85 (6):915-8, 1995.	100% patients with already diagnosed “mild” preeclampsia
Sanchez-Ramos L, Briones DK, Kaunitz AM, Delvalle GO, Gaudier FL, Walker CD. Prevention of pregnancy-induced hypertension by calcium supplementation in angiotensin II-sensitive patients. Obstetrics & Gynecology 84 (3):349-53, 1994.	In Hofmeyer 2007 systematic review
Sanders TA, Purves R. An anthropometric and dietary assessment of the nutritional status of vegan preschool children. Journal of Human Nutrition 35 (5):349-57, 1981.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Sato K, Emoto N, Toraya S et al. Progressively increased serum 1,25-dihydroxyVitamin D2 concentration in a hypoparathyroid patient with protracted hypercalcemia due to Vitamin D2 intoxication. Endocrine Journal 41 (4):329-37, 1994.	Case report

Excluded Study	Reason
Satterfield S, Cutler JA, Langford HG et al. Trials of hypertension prevention. Phase I design. Annals of Epidemiology 1(5):455-71, 1991.	Shows research design, but no result
Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P, Koerfer R. Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial.[see comment]. American Journal of Clinical Nutrition 83 (4):754 -9, 2006.	>=20% subjects with diseases
Schumann SA, Ewigman B. Double-dose Vitamin D lowers cancer risk in women over 55. Journal of Family Practice 2007; 56(11):907-910.	Editorial-like brief review
Sellers TA, Bazyk AE, Bostick RM et al. Diet and risk of colon cancer in a large prospective study of older women: an analysis stratified on family history (Iowa, United States). Cancer Causes & Control 9(4):357-67, 1998.	Same cohort as Zheng 1998 (RefID 2924) only difference is that taking into consideration the family history of colon cancer in the analysis
Shahar DR, Abel R, Elhayany A, Vardi H, Fraser D. Does dairy calcium intake enhance weight loss among overweight diabetic patients? Diabetes Care 2007; 30(3):485-489.	>=20% subjects with diseases
Shapses SA, Heshka S, Heymsfield SB. Effect of calcium supplementation on weight and fat loss in women. Journal of Clinical Endocrinology & Metabolism 89 (2):632-7, 2004.	In systematic review
Sharkey JR, Giuliani C, Haines PS, Branch LG, Busby-Whitehead J, Zohoori N. Summary measure of dietary musculoskeletal nutrient (calcium, Vitamin D, magnesium, and phosphorus) intakes is associated with lower-extremity physical performance in homebound elderly men and women. American Journal of Clinical Nutrition 77 (4):847-56, 2003.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Shaunak S, Ang L, Colston K, Patel S, Bland M, Maxwell JD. Muscle strength in healthy white and Asian subjects: the relationship of quadriceps maximum voluntary contraction to age, sex, body build and Vitamin D. Clinical Science 73 (5):541-6, 1987.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Sibai BM, Ewell M, Levine RJ et al. Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) Study Group. American Journal of Obstetrics & Gynecology 177 (5):1003-10, 1997.	No Ca dose
Sieg J, Sieg A, Dreyhaupt J, Schmidt-Gayk H. Insufficient Vitamin D supply as a possible co-factor in colorectal carcinogenesis. Anticancer Research 26 (4A):2729 -33, 2006.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Silverman SL, Delmas PD, Kulkarni PM, Stock JL, Wong M, Plouffe L, Jr. Comparison of fracture, cardiovascular event, and breast cancer rates at 3 years in postmenopausal women with osteoporosis. Journal of the American Geriatrics Society 52 (9):1543-8, 2004.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Sita-Lumsden A, Lapthorn G, Swaminathan R, Milburn HJ. Reactivation of tuberculosis and Vitamin D deficiency: the contribution of diet and exposure to sunlight. Thorax 62 (11):1003-7, 2007.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Siwek RA, Burkinshaw L, Oxby CB, Robinson PA. Multi-element analysis of the obese subject by in vivo neutron activation analysis. Physics in Medicine & Biology 29 (6):687-701, 1984.	Not relevant
Skinner JD, Bounds W, Carruth BR, Ziegler P. Longitudinal calcium intake is negatively related to children's body fat indexes.. Journal of the American Dietetic Association 103 (12):1626-31, 2003.	Not RCT growth study
Slemenda CW, Reister TK, Hui SL, Miller JZ, Christian JC, Johnston CC, Jr. Influences on skeletal mineralization in children and adolescents: evidence for varying effects of sexual maturation and physical actiVitaminy. Journal of Pediatrics 125 (2):201-7, 1994.	No 25(OH)D or dietary Ca
Specker BL, Beck A, Kalkwarf H, Ho M. Randomized trial of varying mineral intake on total body bone mineral accretion during the first year of life. Pediatrics 99(6): E12, 1997.	No independent Ca effect
Specker BL, Tsang RC, Ho M, Miller D. Effect of vegetarian diet on serum 1,25-dihydroxyVitamin D concentrations during lactation. Obstetrics & Gynecology 70 (6):870-4, 1987.	No 25(OH)D or dietary Ca
Specker BL, Valanis B, Hertzberg V, Edwards N, Tsang RC. Sunshine exposure and serum 25-hydroxyVitamin D concentrations in exclusively breast-fed infants. Journal of Pediatrics 107 (3):372-6, 1985.	Cross-sectional or retrospective assessment of diet after disease diagnosis

Excluded Study	Reason
Stamler J, Liu K, Ruth KJ, Pryer J, Greenland P. Eight-year blood pressure change in middle-aged men: relationship to multiple nutrients. Hypertension 39 (5):1000-6, 2002.	No outcomes of interest
Stern HS, Gregoire RC, Kashtan H, Stadler J, Bruce RW. Long-term effects of dietary calcium on risk markers for colon cancer in patients with familial polyposis. Surgery 108 (3):528-33, 1990.	No outcomes of interest
Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. Diabetic Medicine 2008;25:320-5.	>=20% subjects with diseases
Swanenburg J, de Bruin ED, Stauffacher M, Mulder T, Uebelhart D. Effects of exercise and nutrition on postural balance and risk of falling in elderly people with decreased bone mineral density: randomized controlled trial pilot study. Clinical Rehabilitation 2007; 21(6):523-534.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Takeuchi A, Okano T, Tsugawa N et al. Effects of ergocalciferol supplementation on the concentration of Vitamin D and its metabolites in human milk. Journal of Nutrition 119 (11):1639-46, 1989.	Not RCT arrow 4 study
Tanji JL, Lew EY, Wong GY, Treguboff C, Ward JA, Amsterdam EA. Dietary calcium supplementation as a treatment for mild hypertension.. Journal of the American Board of Family Practice 4(3):145-50, 1991.	In systematic review
Taylor EN, Stampfer MJ, Curhan GC. Dietary factors and the risk of incident kidney stones in men: new insights after 14 years of follow-up. Journal of the American Society of Nephrology 15 (12):3225-32, 2004.	No outcomes of interest
Teegarden D, White KM, Lyle RM et al. Calcium and dairy product modulation of lipid utilization and energy expenditure. Obesity 16 (7):1566-72, 2008.	No outcomes of interest
Thompson IM, Coltman CA, Jr., Crowley J. Chemoprevention of prostate cancer: the Prostate Cancer Prevention Trial. Prostate 33 (3):217-21, 1997.	Commentary
Thompson WG, Rostad HN, Janzow DJ, Slezak JM, Morris KL, Zemel MB. Effect of energy-reduced diets high in dairy products and fiber on weight loss in obese adults. Obesity Research 13(8):1344-53, 2005.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Thomson K, Morley R, Grover SR, Zacharin MR. Postnatal evaluation of Vitamin D and bone health in women who were Vitamin D-deficient in pregnancy, and in their infants.[erratum appears in Med J Aust. 2005 Jan 3;182(1):48 Note: Thompson, Katherine [corrected to Thomson, Katherine]]. Medical Journal of Australia 181 (9):486-8, 2004.	No analysis of association between 25(OH)D and outcomes
Tomoda S, Kitanaka T, Ogita S, Hidaka A. Prevention of pregnancy-induced hypertension by calcium dietary supplement: a preliminary report. Journal of Obstetrics & Gynaecology 21(3):281-8, 1995.	No outcomes of interest
Tretli S, Hernes E, Berg JP, Hestvik UE, Robsahm TE. Association between serum 25(OH)D and death from prostate cancer. British Journal of Cancer 100 (3):450 -4, 2009.	>=20% subjects with diseases
Tsang RC, Gigger M, Oh W, Brown DR. Studies in calcium metabolism in infants with intrauterine growth retardation. Journal of Pediatrics 86 (6):936-41, 1975.	No 25(OH)D or dietary Ca
Tworoger SS, Lee IM, Buring JE, Rosner B, Hollis BW, Hankinson SE. Plasma 25-hydroxyVitamin D and 1,25-dihydroxyVitamin D and risk of incident ovarian cancer. Cancer Epidemiology, Biomarkers & Prevention 2007; 16(4):783-788.	No outcomes of interest
van Beresteijn EC, Riedstra M, van der WA, Schouten EG, Burema J, Kok FJ. Habitual dietary calcium intake and blood pressure change around the menopause: a longitudinal study. International Journal of Epidemiology 21(4):683-9, 1992.	No outcomes of interest
van Buul BJ, Steegers EA, Jongsma HW et al. Dietary sodium restriction in the prophylaxis of hypertensive disorders of pregnancy: effects on the intake of other nutrients. American Journal of Clinical Nutrition 62 (1):49-57, 1995.	Ca intake and BM (mothers and neonates) measured but not assessed ==> no relevant results reported
Vatanparast H, Baxter-Jones A, Faulkner RA, Bailey DA, Whiting SJ. Positive effects of vegetable and fruit consumption and calcium intake on bone mineral accrual in boys during growth from childhood to adolescence: the University of Saskatchewan Pediatric Bone Mineral Accrual Study. American Journal of Clinical Nutrition 82 (3):700-6, 2005.	No 25(OH)D or dietary Ca

Excluded Study	Reason
Vergnaud AC, Peneau S, Chat-Yung S et al. Dairy consumption and 6-y changes in body weight and waist circumference in middle-aged French adults. American Journal of Clinical Nutrition 88 (5):1248 -55, 2008.	not RCT (weight outcome)
Verhaar HJ, Samson MM, Jansen PA, de Vreede PL, Manten JW, Duursma SA. Muscle strength, functional mobility and Vitamin D in older women.. Aging-Clinical & Experimental Research 12 (6):455-60, 2000.	In Ottawa EPC report
Verreault R, Semba RD, Volpato S, Ferrucci L, Fried LP, Guralnik JM. Low serum Vitamin d does not predict new disability or loss of muscle strength in older women. Journal of the American Geriatrics Society 50 (5):912-7, 2002.	In Ottawa EPC report
Verreault R, Semba RD, Volpato S, Ferrucci L, Fried LP, Guralnik JM. Low serum Vitamin d does not predict new disability or loss of muscle strength in older women. Journal of the American Geriatrics Society 50(5):912-7, 2002.	In Ottawa EPC report
Villar J, bdel-Aleem H, Merialdi M et al. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. American Journal of Obstetrics & Gynecology. 194(3):639-49, 2006 Mar.	In Hofmeyer 2007 systematic review, systematic review
Villar J, Gulmezoglu AM, de OM. Nutritional and antimicrobial interventions to prevent preterm birth: an overview of randomized controlled trials. Obstetrical & Gynecological Survey 53 (9):575-85, 1998 Sep.	Not relevant systematic review
Villar J, Repke JT. Calcium supplementation during pregnancy may reduce preterm delivery in high-risk populations. American Journal of Obstetrics & Gynecology 163 (4 Pt 1):1124-31, 1990.	In Hofmeyer 2007 systematic review
Visser M, Deeg DJ, Lips P, Longitudinal Aging SA. Low Vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. Journal of Clinical Endocrinology & Metabolism 88 (12):5766-72, 2003.	In Ottawa EPC report
von Hurst PR, Stonehouse W, Matthys C, Conlon C, Kruger MC, Coad J. Study protocol--metabolic syndrome, vitamin D and bone status in South Asian women living in Auckland, New Zealand: a randomised, placebo-controlled, double-blind vitamin D intervention. BMC Public Health 8 :267, 2008.	RCT protocol only
Wallace K, Baron JA, Cole BF et al. Effect of calcium supplementation on the risk of large bowel polyps.[see comment]. Journal of the National Cancer Institute 96 (12):921-5, 2004.	In Weigarten 2008 SR
Wallace K, Baron JA, Karagas MR et al. The association of physical actiVitaminy and body mass index with the risk of large bowel polyps. Cancer Epidemiology, Biomarkers & Prevention 14(9):2082-6, 2005.	No outcomes of interest
Waltman NL, Twiss JJ, Ott CD et al. Testing an intervention for preventing osteoporosis in postmenopausal breast cancer survivors. Journal of Nursing Scholarship 35 (4):333-8, 2003.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Wanchu M, Malhotra S, Khullar M. Calcium supplementation in pre-eclampsia. Journal of the Association of Physicians of India 49:795-8, 2001.	In Hofmeyer 2007 systematic review
Wang LD, Qiu SL, Yang GR, Lipkin M, Newmark HL, Yang CS. A randomized double-blind intervention study on the effect of calcium supplementation on esophageal precancerous lesions in a high-risk population in China. Cancer Epidemiology, Biomarkers & Prevention 2(1):71-8, 1993.	>=20% subjects with diseases
Wargovich MJ, Isbell G, Shabot M et al. Calcium supplementation decreases rectal epithelial cell proliferation in subjects with sporadic adenoma. Gastroenterology 103 (1):92-7, 1992.	No outcomes of interest
Webb AR, Pilbeam C, Hanafin N, Holick MF. An evaluation of the relative contributions of exposure to sunlight and of diet to the circulating concentrations of 25-hydroxyVitamin D in an elderly nursing home population in Boston. American Journal of Clinical Nutrition 51 (6):1075-81, 1990.	Not RCT arrow 4 study
Webber CE, Blake JM, Chambers LF, Roberts JG. Effects of 2 years of hormone replacement upon bone mass, serum lipids and lipoproteins. Maturitas. 19(1):13-23, 1994 May.	No 25(OH)D or dietary Ca
Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS. Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. Journal of the National Cancer Institute 97 (22):1688-94, 2005.	No 25(OH)D or dietary Ca
Weinberger MH, Wagner UL, Fineberg NS. The blood pressure effects of calcium supplementation in humans of known sodium responsiveness. American Journal of Hypertension 6 (9):799-805, 1993.	In systematic review

Excluded Study	Reason
Weisgerber UM, Boeing H, Owen RW, Waldherr R, Raedsch R, Wahrendorf J. Effect of longterm placebo controlled calcium supplementation on sigmoidal cell proliferation in patients with sporadic adenomatous polyps. Gut 38 (3):396-402, 1996.	No outcomes of interest
Weisman Y, Bawnik JC, Eisenberg Z, Spirer Z. Vitamin D metabolites in human milk. Journal of Pediatrics 100 (5):745-8, 1982.	Cross-sectional or retrospective assessment of diet after disease diagnosis
Weston TL, Aronson KJ, Siemiatycki J, Howe GR, Nadon L. Cancer mortality among males in relation to exposures assessed through a job-exposure matrix. International Journal of Occupational & Environmental Health 6(3):194-202, 2000.	No 25(OH)D or dietary Ca
Widga AC, Lewis NM. Defined, in-home, prenatal nutrition intervention for low-income women. Journal of the American Dietetic Association 99(9):1058-62, 1999.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med 1990; 323(24):1664-1672.	No 25(OH)D or dietary Ca
Williams CP, Child DF, Hudson PR et al. Why oral calcium supplements may reduce renal stone disease: report of a clinical pilot study. Journal of Clinical Pathology 54 (1):54-62, 2001.	No UL outcomes
Wimalawansa SJ. Antihypertensive effects of oral calcium supplementation may be mediated through the potent vasodilator CGRP. American Journal of Hypertension 6 (12):996-1002, 1993.	n=8, Ca to Rx HTN
Witteman JC, Willett WC, Stampfer MJ et al. A prospective study of nutritional factors and hypertension among US women. Circulation 80 (5):1320-7, 1989.	Superceded by Ascherio (4022)
Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of Vitamin D in obesity. [erratum appears in Am J Clin Nutr. 2003 May;77(5):1342]. American Journal of Clinical Nutrition 72 (3):690-3, 2000.	Not RCT arrow 4 study
Wosje KS, Kalkwarf HJ. Lactation, weaning, and calcium supplementation: effects on body composition in postpartum women. American Journal of Clinical Nutrition 80 (2):423-9, 2004.	No outcomes of interest
Wyatt HR, Jortberg BT, Babbel C et al. Weight loss in a community initiative that promotes decreased energy intake and increased physical actiVitaminy and dairy consumption: Calcium Weighs-In. Journal of Physical ActiVitaminy & Health 5(1):28-44, 2008.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Yang YX, Han JH, Shao XP et al. Effect of micronutrient supplementation on the growth of preschool children in China. Biomedical & Environmental Sciences 15 (3):196-202, 2002.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Yesudian PD, Berry JL, Wiles S et al. The effect of ultraviolet B-induced Vitamin D levels on host resistance to Mycobacterium tuberculosis: a pilot study in immigrant Asian adults living in the United Kingdom. Photodermatology, Photoimmunology & Photomedicine 24 (2):97-8, 2008.	No outcomes of interest
Zemel MB, Richards J, Milstead A, Campbell P. Effects of calcium and dairy on body composition and weight loss in African-American adults. Obesity Research 13(7):1218-25, 2005.	In systematic review
Zemel MB, Thompson W, Milstead A, Morris K, Campbell P. Calcium and dairy acceleration of weight and fat loss during energy restriction in obese adults. Obesity Research 12 (4):582-90, 2004.	In systematic review
Zhang Y, Kiel DP, Ellison RC et al. Bone mass and the risk of prostate cancer: the Framingham Study. American Journal of Medicine 113 (9):734-9, 2002.	No 25(OH)D or dietary Ca
Zhou C, Fan S, Zhou L, Ni Y, Huang T, Shi Y. Clinical observation of treatment of hypertension with calcium. American Journal of Hypertension 7 (4 Pt 1):363-7, 1994.	In systematic review
Zofkova I, Hill M. Long-term 1,25(OH)2 Vitamin D therapy increases bone mineral density in osteopenic women. Comparison with the effect of plain Vitamin D. Aging-Clinical & Experimental Research. 19(6):472-7, 2007 Dec.	Combination of Vitamin D/Ca and other treatment w/o analysis of independent effect
Zorbas YG, Petrov KL, Kakurin VJ et al. Calcium supplementation effect on calcium balance in endurance-trained athletes during prolonged hypokinesia and ambulatory conditions. Biological Trace Element Research 73 (3):231-50, 2000.	Arrow 4: calcium balance

Excluded Studies (From the Current Report)

Rejected for Study Design—N=191

1. Abrams SA. Calcium and vitamin D requirements for optimal bone mass during adolescence. Current Opinion in Clinical Nutrition & Metabolic Care. 2011 Nov;14(6):605-9. PMID: 21849894.
2. Adami S, Giannini S, Bianchi G, et al. Vitamin D status and response to treatment in post-menopausal osteoporosis. Osteoporosis International. 2009 Feb;20(2):239-44. PMID: 18551242.
3. Adams SV, Newcomb PA, Burnett-Hartman AN, et al. Circulating 25-hydroxyvitamin-D and risk of colorectal adenomas and hyperplastic polyps. Nutrition & Cancer. 2011;63(3):319-26. PMID: 21432725.
4. Ahn J, Albanes D, Berndt SI, et al. Vitamin D-related genes, serum vitamin D concentrations and prostate cancer risk. Carcinogenesis. 2009 May;30(5):769-76. PMID: 19255064.
5. Allan K, Devereux G. Diet and asthma: nutrition implications from prevention to treatment. Journal of the American Dietetic Association. 2011 Feb;111(2):258-68. PMID: 21272700.
6. Alvarez JA, Ashraf A. Role of vitamin d in insulin secretion and insulin sensitivity for glucose homeostasis. International Journal of Endocrinology Print. 2010;2010:351385. PMID: 20011094.
7. Alzaim M, Wood RJ. Vitamin D and gestational diabetes mellitus. Nutrition Reviews. 2013 Mar;71(3):158-67. PMID: 23452283.
8. Annweiler C, Rolland Y, Schott AM, et al. Higher vitamin D dietary intake is associated with lower risk of alzheimer's disease: a 7-year follow-up. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2012 Nov;67(11):1205-11. PMID: 22503994.
9. Annweiler C, Schott A-M, Montero-Odasso M, et al. Cross-sectional association between serum vitamin D concentration and walking speed measured at usual and fast pace among older women: the EPIDOS study. Journal of Bone & Mineral Research. 2010 Aug;25(8):1858-66. PMID: 20205167.
10. Assimos D. Re: Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. Journal of Urology. 2011 Nov;186(5):1918. PMID: 21993105.
11. Attar SM. Vitamin D deficiency in rheumatoid arthritis. Prevalence and association with disease activity in Western Saudi Arabia. Saudi Medical Journal. 2012 May;33(5):520-5. PMID: 22588813.
12. Barake R, Weiler H, Payette H, et al. Vitamin D supplement consumption is required to achieve a minimal target 25-hydroxyvitamin D concentration of > or = 75 nmol/L in older people. Journal of Nutrition. 2010 Mar;140(3):551-6. PMID: 20089782.

13. Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, et al. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. Journal of Bone & Mineral Research. 2009 May;24(5):935-42. PMID: 19113911.

14. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, et al. Benefit-risk assessment of vitamin D supplementation. Osteoporosis International. 2010 Jul;21(7):1121-32. PMID: 19957164.

15. Bolland MJ, Grey A, Avenell A, et al. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ. 2011;342:d2040. PMID: 21505219.

16. Boyce AM, Gafni RI. Approach to the child with fractures. Journal of Clinical Endocrinology & Metabolism. 2011 Jul;96(7):1943-52. PMID: 21734001.

17. Chaganti RK, Parimi N, Cawthon P, et al. Association of 25-hydroxyvitamin D with prevalent osteoarthritis of the hip in elderly men: the osteoporotic fractures in men study. Arthritis & Rheumatism. 2010 Feb;62(2):511-4. PMID: 20112402.

18. Chai W, Maskarinec G, Cooney RV. Serum 25-hydroxyvitamin D levels and mammographic density among premenopausal women in a multiethnic population. European Journal of Clinical Nutrition. 2010 Jun;64(6):652-4. PMID: 20216557.

19. Christenson ES, Jiang X, Kagan R, et al. Osteoporosis management in post-menopausal women. Minerva Ginecologica. 2012 Jun;64(3):181-94. PMID: 22635014.

20. Coney P, Demers LM, Dodson WC, et al. Determination of vitamin D in relation to body mass index and race in a defined population of black and white women. International Journal of Gynaecology & Obstetrics. 2012 Oct;119(1):21-5. PMID: 22818533.

21. Dasgupta A, Saikia U, Sarma D. Status of 25(OH)D levels in pregnancy: A study from the North Eastern part of India. Indian Journal of Endocrinology and Metabolism. 2012 Dec;16(Suppl 2):S405-7. PMID: 23565444.

22. Davis LM, Chang S-C, Mancini J, et al. Vitamin D insufficiency is prevalent among pregnant African American adolescents. Journal of Pediatric & Adolescent Gynecology. 2010 Feb;23(1):45-52. PMID: 19643639.

23. Davis W, Rockway S, Kwasny M. Effect of a combined therapeutic approach of intensive lipid management, omega-3 fatty acid supplementation, and increased serum 25 (OH) vitamin D on coronary calcium scores in asymptomatic adults. American Journal of Therapeutics. 2009 Jul-Aug;16(4):326-32. PMID: 19092644.

24. Dunlop AL, Taylor RN, Tangpricha V, et al. Maternal micronutrient status and preterm versus term birth for black and white US women. Reproductive Sciences. 2012 Sep;19(9):939-48. PMID: 22527984.

25. El Hayek J, Egeland G, Weiler H. Older age and lower adiposity predict better 25-hydroxy vitamin D concentration in Inuit adults: International Polar Year Inuit Health Survey, 2007-2008. Archives of Osteoporosis. 2011 Dec;6(1-2):167-77. PMID: 22886103.

26. Ertl R, Yu CKH, Samaha R, et al. Maternal serum vitamin D at 11-13 weeks in pregnancies delivering small for gestational age neonates. Fetal Diagnosis & Therapy. 2012;31(2):103-8. PMID: 22261570.

27. Esteitie R, Naclerio RM, Baroody FM. Vitamin D levels in children undergoing adenotonsillectomies. International Journal of Pediatric Otorhinolaryngology. 2010 Sep;74(9):1075-7. PMID: 20638140.

28. Fairweather-Tait SJ, Skinner J, Guile GR, et al. Diet and bone mineral density study in postmenopausal women from the TwinsUK registry shows a negative association with a traditional English dietary pattern and a positive association with wine. American Journal of Clinical Nutrition. 2011 Nov;94(5):1371-5. PMID: 21940596.

29. Fall T, Shiue I, Bergea af Geijerstam P, et al. Relations of circulating vitamin D concentrations with left ventricular geometry and function. European Journal of Heart Failure. 2012 Sep;14(9):985-91. PMID: 22723659.

30. Formiga F, Ferrer A, Almeda J, et al. Utility of geriatric assessment tools to identify 85-years old subjects with vitamin D deficiency. Journal of Nutrition, Health & Aging. 2011 Feb;15(2):110-4. PMID: 21365163.

31. Gallicchio L, Helzlsouer KJ, Chow W-H, et al. Circulating 25-hydroxyvitamin D and the risk of rarer cancers: Design and methods of the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. American Journal of Epidemiology. 2010 Jul 1;172(1):10-20. PMID: 20562188.

32. Garg M, Lubel JS, Sparrow MP, et al. Review article: vitamin D and inflammatory bowel disease--established concepts and future directions. Alimentary Pharmacology & Therapeutics. 2012 Aug;36(4):324-44. PMID: 22686333.

33. Garrett-Mayer E, Wagner CL, Hollis BW, et al. Vitamin D3 supplementation (4000 IU/d for 1 y) eliminates differences in circulating 25-hydroxyvitamin D between African American and white men. American Journal of Clinical Nutrition. 2012 Aug;96(2):332-6. PMID: 22760568.

34. Geleijnse JM. Vitamin D and the prevention of hypertension and cardiovascular diseases: a review of the current evidence. American Journal of Hypertension. 2011 Mar;24(3):253-62. PMID: 20847727.

35. Genuis SJ, Bouchard TP. Combination of Micronutrients for Bone (COMB) Study: bone density after micronutrient intervention. Journal Of Environmental & Public Health. 2012;2012:354151. PMID: 22291722.

36. Gilbert R, Martin RM, Fraser WD, et al. Predictors of 25-hydroxyvitamin D and its association with risk factors for prostate cancer: evidence from the prostate testing for cancer and treatment study. Cancer Causes & Control. 2012 Apr;23(4):575-88. PMID: 22382867.

37. Gilbert R, Metcalfe C, Fraser WD, et al. Associations of circulating retinol, vitamin E, and 1,25-dihydroxyvitamin D with prostate cancer diagnosis, stage, and grade. Cancer Causes & Control. 2012 Nov;23(11):1865-73. PMID: 22926301.

38. Gilbert R, Metcalfe C, Fraser WD, et al. Associations of circulating 25-hydroxyvitamin D with prostate cancer diagnosis, stage and grade. International Journal of Cancer. 2012 Sep 1;131(5):1187-96. PMID: 22033893.

39. Ginde AA, Camargo CA, Jr., Shapiro NI. Vitamin D insufficiency and sepsis severity in emergency department patients with suspected infection. Academic Emergency Medicine. 2011 May;18(5):551-4. PMID: 21518095.

40. Goleva E, Searing DA, Jackson LP, et al. Steroid requirements and immune associations with vitamin D are stronger in children than adults with asthma. Journal of Allergy & Clinical Immunology. 2012 May;129(5):1243-51. PMID: 22330698.

41. Goltz L, Degenhardt G, Maywald U, et al. Evaluation of a program of integrated care to reduce recurrent osteoporotic fractures. Pharmacoepidemiology & Drug Safety. 2013 Mar;22(3):263-70. PMID: 23296590.

42. Gominak SC, Stumpf WE. The world epidemic of sleep disorders is linked to vitamin D deficiency. Medical Hypotheses. 2012 Aug;79(2):132-5. PMID: 22583560.

43. Gonzalez CA, Riboli E. Diet and cancer prevention: Contributions from the European Prospective Investigation into Cancer and Nutrition (EPIC) study. European Journal of Cancer. 2010 Sep;46(14):2555-62. PMID: 20843485.

44. Grant WB, Schwalfenberg GK, Genuis SJ, et al. An estimate of the economic burden and premature deaths due to vitamin D deficiency in Canada. Molecular Nutrition & Food Research. 2010 Aug;54(8):1172-81. PMID: 20352622.

45. Grant WB, Tangpricha V. Vitamin D: Its role in disease prevention. Dermato-endocrinology. 2012 Apr 1;4(2):81-3. PMID: 22928061.

46. Guerrieri-Gonzaga A, Gandini S. Vitamin D and overall mortality. Pigment Cell & Melanoma Research. 2013 Jan;26(1):16-28. PMID: 23045997.

47. Hansen KE. High-dose vitamin D: helpful or harmful? Current Rheumatology Reports. 2011 Jun;13(3):257-64. PMID: 21369796.

48. Harvey NC, Javaid K, Bishop N, et al. MAVIDOS Maternal Vitamin D Osteoporosis Study: study protocol for a randomized controlled trial. The MAVIDOS Study Group. Trials [Electronic Resource]. 2012;13:13. PMID: 22314083.

49. Holmes VA, Barnes MS, Alexander HD, et al. Vitamin D deficiency and insufficiency in pregnant women: a longitudinal study. British Journal of Nutrition. 2009 Sep;102(6):876-81. PMID: 19331703.

50. Hronek M, Doubkova P, Hrnciarikova D, et al. Dietary intake of energy and nutrients in relation to resting energy expenditure and anthropometric parameters of Czech pregnant women. European Journal of Nutrition. 2013 Feb;52(1):117-25. PMID: 22198818.

51. Huang W, Shah S, Long Q, et al. Improvement of pain, sleep, and quality of life in chronic pain patients with vitamin d supplementation. Clinical Journal of Pain. 2013 Apr;29(4):341-7. PMID: 22699141.

52. Jin S-E, Park J-S, Kim C-K. Pharmacokinetics of oral calcitriol in healthy human based on the analysis with an enzyme immunoassay. Pharmacological Research. 2009 Jul;60(1):57-60. PMID: 19427587.

53. Jyvakorpi SK, Puranen T, Pitkala KH, et al. Nutritional treatment of aged individuals with Alzheimer disease living at home with their spouses: study protocol for a randomized controlled trial. Trials [Electronic Resource]. 2012;13:66. PMID: 22624652.

54. Kalava UR, Cha SS, Takahashi PY. Association between vitamin D and pressure ulcers in older ambulatory adults: results of a matched case-control study. Clinical Interventions In Aging. 2011;6:213-9. PMID: 21966215.

55. Karatekin G, Kaya A, Salihoglu O, et al. Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers. European Journal of Clinical Nutrition. 2009 Apr;63(4):473-7. PMID: 18030309.

56. Kaukonen J-P, Luthje P, Nurmi-Luthje I, et al. Second hip fracture and patients' medication after the first hip fracture: a follow-up of 221 hip fracture patients in Finland. Archives of Gerontology & Geriatrics. 2011 Mar-Apr;52(2):185-9. PMID: 20399516.

57. Kawase T, Matsuo K, Suzuki T, et al. Association between vitamin D and calcium intake and breast cancer risk according to menopausal status and receptor status in Japan. Cancer Science. 2010 May;101(5):1234-40. PMID: 20151981.

58. Khader YS, Batieha A, Jaddou H, et al. Relationship between 25-hydroxyvitamin D and metabolic syndrome among Jordanian adults. Nutrition Research & Practice. 2011 Apr;5(2):132-9. PMID: 21556227.

59. Kluczynski MA, Lamonte MJ, Mares JA, et al. Duration of physical activity and serum 25-hydroxyvitamin D status of postmenopausal women. Annals of Epidemiology. 2011 Jun;21(6):440-9. PMID: 21414803.

60. Koul PA, Ahmad SH, Ahmad F, et al. Vitamin d toxicity in adults: a case series from an area with endemic hypovitaminosis d. Oman Medical Journal. 2011 May;26(3):201-4. PMID: 22043417.

61. Kuchuk NO, van Schoor NM, Pluijm SM, et al. Vitamin D status, parathyroid function, bone turnover, and BMD in postmenopausal women with osteoporosis: global perspective. Journal of Bone & Mineral Research. 2009 Apr;24(4):693-701. PMID: 19049341.

62. Lamendola CA, Ariel D, Feldman D, et al. Relations between obesity, insulin resistance, and 25-hydroxyvitamin D. American Journal of Clinical Nutrition. 2012 May;95(5):1055-9. PMID: 22440850.

63. Lee P, Greenfield JR, Seibel MJ, et al. Adequacy of vitamin D replacement in severe deficiency is dependent on body mass index. American Journal of Medicine. 2009 Nov;122(11):1056-60. PMID: 19854337.

64. Li B, Byrjalsen I, Glendenning P, et al. Selective monitoring of vitamin D2 and D3 supplementation with a highly specific 25-hydroxyvitamin D3 immunoassay with negligible cross-reactivity to 25-hydroxyvitamin D2. Clinica Chimica Acta. 2009 Jun 27;404(2):144-8. PMID: 19336231.

65. Liang L, Chantry C, Styne DM, et al. Prevalence and risk factors for vitamin D deficiency among healthy infants and young children in Sacramento, California. European Journal of Pediatrics. 2010 Nov;169(11):1337-44. PMID: 20532799.

66. Lim S, Shin H, Kim MJ, et al. Vitamin D inadequacy is associated with significant coronary artery stenosis in a community-based elderly cohort: the Korean Longitudinal Study on Health and Aging. Journal of Clinical Endocrinology & Metabolism. 2012 Jan;97(1):169-78. PMID: 22013101.

67. Linday LA. Cod liver oil, young children, and upper respiratory tract infections. Journal of the American College of Nutrition. 2010 Dec;29(6):559-62. PMID: 21677119.

68. Litonjua AA. Vitamin D deficiency as a risk factor for childhood allergic disease and asthma. Current Opinion in Allergy & Clinical Immunology. 2012 Apr;12(2):179-85. PMID: 22266772.

69. Liu K, Meng H, Tang X, et al. Elevated plasma calcifediol is associated with aggressive periodontitis. Journal of Periodontology. 2009 Jul;80(7):1114-20. PMID: 19563291.

70. Lopez-Torres Hidalgo J, Group A. Prevention of falls and fractures in old people by administration of calcium and vitamin D, randomized clinical trial. BMC Public Health. 2011;11:910. PMID: 22151975.

71. Luzzi R, Belcaro G, Cornelli U, et al. Osteoporosis of the jaw. Product evaluation: mf Odontovis Calcium. Panminerva Medica. 2011 Sep;53(3 Suppl 1):83-7. PMID: 22108482.

72. Mahdy S, Al-Emadi SA, Khanjar IA, et al. Vitamin D status in health care professionals in Qatar. Saudi Medical Journal. 2010 Jan;31(1):74-7. PMID: 20062904.

73. Maji D. Vitamin D toxicity. Indian Journal of Endocrinology and Metabolism. 2012 Mar;16(2):295-6. PMID: 22470872.

74. Makariou S, Liberopoulos E, Florentin M, et al. The relationship of vitamin D with non-traditional risk factors for cardiovascular disease in subjects with metabolic syndrome. Archives of Medical Science. 2012 Jul 4;8(3):437-43. PMID: 22851997.

75. Makgoba M, Nelson SM, Savvidou M, et al. First-trimester circulating 25-hydroxyvitamin D levels and development of gestational diabetes mellitus. Diabetes Care. 2011 May;34(5):1091-3. PMID: 21454797.

76. Manickam B, Washington T, Villagrana NE, et al. Determinants of circulating 25-hydroxyvitamin D and bone mineral density in young physicians. Endocrine Practice. 2012 Mar-Apr;18(2):219-26. PMID: 22440992.

77. Manson JE, Bassuk SS, Lee IM, et al. The VITamin D and OmegA-3 TriaL (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. Contemporary Clinical Trials. 2012 Jan;33(1):159-71. PMID: 21986389.

78. Mark S, Lambert M, Delvin EE, et al. Higher vitamin D intake is needed to achieve serum 25(OH)D levels greater than 50 nmol/l in Quebec youth at high risk of obesity. European Journal of Clinical Nutrition. 2011 Apr;65(4):486-92. PMID: 21364606.

79. Marwaha RK, Puri S, Tandon N, et al. Effects of sports training & nutrition on bone mineral density in young Indian healthy females. Indian Journal of Medical Research. 2011 Sep;134:307-13. PMID: 21985813.

80. Mathei C, Van Pottelbergh G, Vaes B, et al. No relation between vitamin D status and physical performance in the oldest old: results from the Belfrail study. Age & Ageing. 2013 Mar;42(2):186-90. PMID: 23360776.

81. Miettinen ME, Reinert L, Kinnunen L, et al. Serum 25-hydroxyvitamin D level during early pregnancy and type 1 diabetes risk in the offspring. Diabetologia. 2012 May;55(5):1291-4. PMID: 22270224.

82. Mohr SB, Gorham ED, Alcaraz JE, et al. Serum 25-hydroxyvitamin D and breast cancer in the military: a case-control study utilizing pre-diagnostic serum. Cancer Causes & Control. 2013 Mar;24(3):495-504. PMID: 23296455.

83. Mondul AM, Weinstein SJ, Horst RL, et al. Serum vitamin D and risk of bladder cancer in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial. Cancer Epidemiology, Biomarkers & Prevention. 2012 Jul;21(7):1222-5. PMID: 22623707.

84. Moore WC, Pascual RM. Update in asthma 2009. American Journal of Respiratory & Critical Care Medicine. 2010 Jun 1;181(11):1181-7. PMID: 20516492.

85. Moser AM, Salzer HJF, Krause R. Immunoplasticity--triggers of regulatory function. Medical Hypotheses. 2011 Dec;77(6):1145-7. PMID: 21968277.

86. Mowry DA, Costello MM, Heelan KA. Association among cardiorespiratory fitness, body fat, and bone marker measurements in healthy young females. Journal of the American Osteopathic Association. 2009 Oct;109(10):534-9. PMID: 19861594.

87. Mullins RJ, Clark S, Wiley V, et al. Neonatal vitamin D status and childhood peanut allergy: a pilot study. Annals of Allergy, Asthma, & Immunology. 2012 Nov;109(5):324-8. PMID: 23062387.

88. Munns CF, Simm PJ, Rodda CP, et al. Incidence of vitamin D deficiency rickets among Australian children: an Australian Paediatric Surveillance Unit study. Medical Journal of Australia. 2012 Apr 16;196(7):466-8. PMID: 22509879.

89. Mutlu A, Mutlu GY, Ozsu E, et al. Vitamin D deficiency in children and adolescents with type 1 diabetes. Journal of clinical research in pediatric endocrinology. 2011;3(4):179-83. PMID: 22155459.

90. Nakano T, Tsugawa N, Kuwabara A, et al. High prevalence of hypovitaminosis D and K in patients with hip fracture. Asia Pacific Journal of Clinical Nutrition. 2011;20(1):56-61. PMID: 21393111.

91. Pandita KK, Razdan S, Kudyar RP, et al. “Excess gooD can be Dangerous”. A case series of iatrogenic symptomatic hypercalcemia due to hypervitaminosis D. Clinical Cases in Mineral & Bone Metabolism. 2012 May;9(2):118-20. PMID: 23087723.

92. Perez-Rossello JM, Feldman HA, Kleinman PK, et al. Rachitic changes, demineralization, and fracture risk in healthy infants and toddlers with vitamin D deficiency. Radiology. 2012 Jan;262(1):234-41. PMID: 22106354.

93. Peters S, Adams A. Vitamin D supplementation to reduce the risk of falls and fractures: the dosing dilemma. Orthopedics. 2010 Oct;33(10):748-51. PMID: 20954621.

94. Pilz S, Henry RMA, Snijder MB, et al. Vitamin D deficiency and myocardial structure and function in older men and women: the Hoorn study. Journal of Endocrinological Investigation. 2010 Oct;33(9):612-7. PMID: 20208455.

95. Ponda MP, Huang X, Odeh MA, et al. Vitamin D may not improve lipid levels: a serial clinical laboratory data study. Circulation. 2012 Jul 17;126(3):270-7. PMID: 22718799.

96. Rajakumar K, de las Heras J, Lee S, et al. 25-hydroxyvitamin D concentrations and in vivo insulin sensitivity and cell function relative to insulin sensitivity in black and white youth. Diabetes Care. 2012 Mar;35(3):627-33. PMID: 22238280.

97. Richart T, Thijs L, Nawrot T, et al. The metabolic syndrome and carotid intima-media thickness in relation to the parathyroid hormone to 25-OH-D(3) ratio in a general population. American Journal of Hypertension. 2011 Jan;24(1):102-9. PMID: 20596035.

98. Ring SM, Dannecker EA, Peterson CA. Vitamin d status is not associated with outcomes of experimentally-induced muscle weakness and pain in young, healthy volunteers. Journal of Nutrition and Metabolism. 2010;2010:674240. PMID: 21209718.

99. Rooze S, Dramaix-Wilmet M, Mathieu F, et al. Growth, nutritional status, and signs of rickets in 0-5-year-old children in a Kashin-Beck disease endemic area of Central Tibet. European Journal of Pediatrics. 2012 Aug;171(8):1185-91. PMID: 22354482.

100. Rubin CD. Evaluation and management of hip fracture risk in the aged. American Journal of the Medical Sciences. 2012 Mar;343(3):233-42. PMID: 21629043.

101. Sanford M, McCormack PL. Spotlight on eldecalcitol in osteoporosis.[Reprint of Drugs. 2011 Sep 10;71(13):1755-70; PMID: 21902297]. Drugs & Aging. 2012 Jan 1;29(1):69-71. PMID: 22191725.

102. Schmitz KJ, Skinner HG, Bautista LE, et al. Association of 25-hydroxyvitamin D with blood pressure in predominantly 25-hydroxyvitamin D deficient Hispanic and African Americans. American Journal of Hypertension. 2009 Aug;22(8):867-70. PMID: 19444222.

103. Shin M, Minden C. Evaluation of the effectiveness of cholecalciferol in long-term care elderly patients with hypovitaminosis d. Consultant Pharmacist. 2011 Feb;26(2):101-7. PMID: 21310707.

104. Skinner HG, Litzelman K, Schwartz GG. Recent clinical trials of vitamin D3 supplementation and serum calcium levels in humans: Implications for vitamin D-based chemoprevention. Current Opinion in Investigational Drugs. 2010 Jun;11(6):678-87. PMID: 20496263.

105. Speroff L. Research in a community hospital: some lessons from the Clarkson-Schnatz mentor-mentee pair in The North American Menopause Society Mentorship Program. Menopause. 2011 Feb;18(2):119-20. PMID: 21245774.

106. Stewart JW, Alekel DL, Ritland LM, et al. Serum 25-hydroxyvitamin D is related to indicators of overall physical fitness in healthy postmenopausal women. Menopause. 2009 Nov-Dec;16(6):1093-101. PMID: 19512949.

107. Sun Z, Wang PP, Roebothan B, et al. Calcium and vitamin D and risk of colorectal cancer: results from a large population-based case-control study in Newfoundland and Labrador and Ontario. Canadian Journal of Public Health. Revue Canadienne de Sante Publique. 2011 Sep-Oct;102(5):382-9. PMID: 22032106.

108. Takahashi R, Mizoue T, Otake T, et al. Circulating vitamin D and colorectal adenomas in Japanese men. Cancer Science. 2010 Jul;101(7):1695-700. PMID: 20507319.

109. Tarcin O, Yavuz DG, Ozben B, et al. Effect of vitamin D deficiency and replacement on endothelial function in asymptomatic subjects. Journal of Clinical Endocrinology & Metabolism. 2009 Oct;94(10):4023-30. PMID: 19584181.

110. Tran B, Armstrong BK, Carlin JB, et al. Recruitment and results of a pilot trial of vitamin D supplementation in the general population of Australia. Journal of Clinical Endocrinology & Metabolism. 2012 Dec;97(12):4473-80. PMID: 23066119.

111. Ubbenhorst A, Striebich S, Lang F, et al. Exploring the relationship between vitamin D and basic personality traits. Psychopharmacology. 2011 Jun;215(4):733-7. PMID: 21274699.

112. Valtuena J, Gracia-Marco L, Vicente-Rodriguez G, et al. Vitamin D status and physical activity interact to improve bone mass in adolescents. The HELENA Study. Osteoporosis International. 2012 Aug;23(8):2227-37. PMID: 22237816.

113. Voloc A, Esterle L, Nguyen TM, et al. High prevalence of genu varum/valgum in European children with low vitamin D status and insufficient dairy products/calcium intakes. European Journal of Endocrinology. 2010 Nov;163(5):811-7. PMID: 20739417.

114. Wu AC, Tantisira K, Li L, et al. Effect of vitamin D and inhaled corticosteroid treatment on lung function in children. American Journal of Respiratory & Critical Care Medicine. 2012 Sep 15;186(6):508-13. PMID: 22798322.

115. Wu K, Feskanich D, Fuchs CS, et al. Interactions between plasma levels of 25-hydroxyvitamin D, insulin-like growth factor (IGF)-1 and C-peptide with risk of colorectal cancer. PLoS ONE [Electronic Resource]. 2011;6(12):e28520. PMID: 22216097.

116. Yamaji T, Iwasaki M, Sasazuki S, et al. Association between plasma 25-hydroxyvitamin D and colorectal adenoma according to dietary calcium intake and vitamin D receptor polymorphism. American Journal of Epidemiology. 2012 Feb 1;175(3):236-44. PMID: 22193171.

117. Yao S, Zirpoli G, Bovbjerg DH, et al. Variants in the vitamin D pathway, serum levels of vitamin D, and estrogen receptor negative breast cancer among African-American women: a case-control study. Breast Cancer Research. 2012;14(2):R58. PMID: 22480149.

118. Yli-Kyyny T, Tamminen I, Syri J, et al. Bilateral hip pain. Lancet. 2011 Jun 25;377(9784):2248. PMID: 21704874.

119. Zablotska LB, Gong Z, Wang F, et al. Vitamin D, calcium, and retinol intake, and pancreatic cancer in a population-based case-control study in the San Francisco Bay area. Cancer Causes & Control. 2011 Jan;22(1):91-100. PMID: 21072578.

120. Zagura M, Serg M, Kampus P, et al. Aortic stiffness and vitamin D are independent markers of aortic calcification in patients with peripheral arterial disease and in healthy subjects. European Journal of Vascular & Endovascular Surgery. 2011 Nov;42(5):689-95. PMID: 21871824.

121. Zhang X, Meng H, Sun X, et al. Elevation of vitamin D-binding protein levels in the plasma of patients with generalized aggressive periodontitis. Journal of Periodontal Research. 2013 Feb;48(1):74-9. PMID: 22803589.

122. Zhao J, Xia W, Nie M, et al. The levels of bone turnover markers in Chinese postmenopausal women: Peking Vertebral Fracture study. Menopause. 2011 Nov;18(11):1237-43. PMID: 21747303.

123. Zittermann A, Prokop S, Gummert JF, et al. Safety issues of vitamin d supplementation. Current Medicinal Chemistry—Anti-Cancer Agents. 2013 Jan 1;13(1):4-10. PMID: 23094916.

124. Wagner CL, Johnson D, Hulsey TC, et al. Vitamin D supplementation during pregnancy Part I NICHD/CTSA randomized clinical trial (RCT): safety consideration. Pediatric Academic Societies Annual Meeting; 2010 May 1-4; Vancouver, Canada; 2010.

125. Wagner CL, Johnson D, Hulsey TC, et al. Vitamin D supplementation during pregnancy part 2 NICHD/CTSA randomized clinical trial (RCT): outcomes. Pediatric Academic Societies' 2010 Annual Meeting; 2010 May 1-4; Vancouver, Canada; 2010.

126. Wagner CL, McNeil R, Hamilton SA, et al. Vitamin D (vitD) supplementation during pregnancy: Thrasher Research Fund RCT in SC community center networks. Pediatric Academic Societies' 2010 Annual Meeting; 2010 May 1-4; Vancouver, Canada; 2010.

127. Breitenbucher A, Voit U, Miedinger D, et al. Substitution of vitamin D in patients with moderate to severe persistent asthma: A randomized, placebo-controlled pilot study [Abstract]. European Respiratory Journal: European Respiratory Society Annual Congress, Vienna, Austria, September 1-5; 2012. p. 857s [4698].

128. Hurst PR, Stonehouse W, Matthys C, et al. Study protocol--metabolic syndrome, vitamin D and bone status in South Asian women living in Auckland, New Zealand: a randomised, placebo-controlled, double-blind vitamin D intervention. BMC public health; 2008. p. 267.

129. Piura E, Chapman JW, Lipton A, et al. Serum 1-OH vitamin D (D) and prognosis of postmenopausal breast cancer (BC) patients: NCIC-CTG MA14 trial [abstract no. 534]. Journal of Clinical Oncology; 2009. p. 15.

130. Lewis E, Fernandez C, Nella AA, et al. The relationship of vitamin D and asthma in children [Abstract]. Journal of Allergy and Clinical Immunology; 2011. p. Ab262.

131. Roth DEA-MAEASRRBREBAH. Randomized Pilot Trial of Two Oral Vitamin D3 Supplementation Regimens during the Third Trimester of Pregnancy in Bangladeshi Women: Effects on Neonatal Vitamin D Status and Safety. Pediatric academic societies annual meeting; 2011 April 28–May 1;Boston MA, United States; 2011.

132. Hanson CKALLEA-BA. Parathyroid Hormone Is Inversely Associated with Low 25(OH)D Levels in Late Preterm Infants at Discharge from the NICU. Pediatric academic societies annual meeting; 2011 April 28–May 1; Boston MA, United States; 2011.

133. Ala-Houhala MJ, Vahavihu K, Kautiainen H, et al. Narrow-band ultraviolet b exposures and oral vitamin d substitution in the treatment of vitamin d insufficiency (Abstract 627). Conference: 41st Annual Meeting of the European Society for Dermatological Research, ESDR 2011 Barcelona Spain. Conference Start: 20110907 Conference End: 20110910. Conference Publication. Journal of investigative dermatology; 2011. p. S105.

134. Jarvenpaa J, Schwab U, Lappalainen T, et al. Mineral water fortified with folic acid and vitamins B6, B12, D and calcium improves folate status and decreases plasma homocysteine concentration in pregnant women. 35th Nordic Congress of Obstetrics and Gynecology; 2006 May 23-25; Goteburg, Sweden; 2008. p. 55.

135. Raggi P, Guasch A. Mineral metabolism and vascular effects of Vitamin D therapy in kidney. clinicaltrials.gov/ct2/show/NCT00646282; 2011.

136. Litonjua AA, Hollis BW, Scheumann BK, et al. Low serum vitamin D levels are associated with increased asthma exacerbations among children using regular inhaled corticosteroids [Abstract]. Journal of Allergy and Clinical Immunology; 2008. p. S144 [555].

137. Christensen P, Riecke BF, Bliddal H, et al. Improved nutritional status after a weight loss formula diet: a cohort study exploring safety in a randomised controlled trial. Obesity Reviews; 2010. p. 247.

138. Das V, Agarwal A, Bhatia V, et al. Evaluation of vitamin d status and need for supplementation in pregnant women of a rural area of North India. International Journal of Gynaecology and Obstetrics; 2009. p. S151.

139. Bilenko N, Belmaker I, Vardi H, et al. Efficacy of multiple micronutrient supplementations on child health: study design and baseline characteristics. The Israel Medical Association journal : IMAJ; 2010. p. 342-7.

140. Thijs W, Janssen K, Verhoosel RM, et al. Effect of vitamin D treatment on antimicrobial peptides in asthma patients and healthy controls [Abstract]. European Respiratory Society Annual Congress, Amsterdam, The Netherlands, September 24-28; 2011. p. 890s [4888].

141. Koo W, Du W. Effect of Vitamin D Status on Bone Mass and Bone Biomarker in Preterm Infants. Pediatric Academic Societies Annual Meeting; 2009 May 2 5; Baltimore MD, United States; 2009.

142. Astrup PCRFHBBFREMBMHTJSHGKWA, Christensen R. Cardiovascular risk factor changes following three different maintenance programs in obese knee osteoarthritis patients after a major weight loss: A randomized controlled trial [abstract]. Osteoarthritis and cartilage; 2012. p. S280.

143. Sahota H. Association of vitamin D related information from a telephone interview with 25-hydroxyvitamin D. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology; 2008. p. 232-8.

144. Hansen TLFHMAB, Pedersen EB. Antihypertensive effect of cholecalciferol during winter months in patients with hypertension [abstract]. Nephrology, dialysis, transplantation; 2012. p. ii89.

145. Abbas S, Linseisen J, Slanger T, et al. The Gc2 allele of the vitamin D binding protein is associated with a decreased postmenopausal breast cancer risk, independent of the vitamin D status. Cancer Epidemiology, Biomarkers & Prevention. 2008 Jun;17(6):1339-43. PMID: 18559548.

146. Abbas S, Nieters A, Linseisen J, et al. Vitamin D receptor gene polymorphisms and haplotypes and postmenopausal breast cancer risk. Breast Cancer Research. 2008;10(2):R31. PMID: 18419802.

147. Bener A, Alsaied A, Al-Ali M, et al. Impact of lifestyle and dietary habits on hypovitaminosis D in type 1 diabetes mellitus and healthy children from Qatar, a sun-rich country. Annals of Nutrition & Metabolism. 2008;53(3-4):215-22. PMID: 19077420.

148. Bischoff-Ferrari HA, Can U, Staehelin HB, et al. Severe vitamin D deficiency in Swiss hip fracture patients. Bone. 2008 Mar;42(3):597-602. PMID: 18180211.

149. Blackmore KM, Lesosky M, Barnett H, et al. Vitamin D from dietary intake and sunlight exposure and the risk of hormone-receptor-defined breast cancer. American Journal of Epidemiology. 2008 Oct 15;168(8):915-24. PMID: 18756015.

150. Giovannucci E. Vitamin D status and cancer incidence and mortality. Advances in Experimental Medicine & Biology. 2008;624:31-42. PMID: 18348445.

151. Granado-Lorencio F, Olmedilla-Alonso B, Herrero-Barbudo C, et al. Seasonal variation of serum alpha- and beta-cryptoxanthin and 25-OH-vitamin D(3) in women with osteoporosis. Osteoporosis International. 2008 May;19(5):717-20. PMID: 17882465.

152. Harinarayan CV, Ramalakshmi T, Prasad UV, et al. Vitamin D status in Andhra Pradesh: a population based study. Indian Journal of Medical Research. 2008 Mar;127(3):211-8. PMID: 18497434.

153. Lehtonen-Veromaa M, Mottonen T, Leino A, et al. Prospective study on food fortification with vitamin D among adolescent females in Finland: minor effects. British Journal of Nutrition. 2008 Aug;100(2):418-23. PMID: 18275625.

154. Makitie O, Toiviainen-Salo S, Marttinen E, et al. Metabolic control and growth during exclusive growth hormone treatment in X-linked hypophosphatemic rickets. Hormone Research. 2008;69(4):212-20. PMID: 18204268.

155. Mizoue T, Kimura Y, Toyomura K, et al. Calcium, dairy foods, vitamin D, and colorectal cancer risk: the Fukuoka Colorectal Cancer Study. Cancer Epidemiology, Biomarkers & Prevention. 2008 Oct;17(10):2800-7. PMID: 18843026.

156. O'Riordan MN, Kiely M, Higgins JR, et al. Prevalence of suboptimal vitamin D status during pregnancy. Irish Medical Journal. 2008 Sep;101(8):240, 2-3. PMID: 18990953.

157. Schwalfenberg G. Vitamin D and diabetes: improvement of glycemic control with vitamin D3 repletion. Canadian Family Physician. 2008 Jun;54(6):864-6. PMID: 18556494.

158. Warner AE, Arnspiger SA. Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. JCR: Journal of Clinical Rheumatology. 2008 Feb;14(1):12-6. PMID: 18431091.

159. Leu JP, Weiner A, Barzel US. Vitamin D toxicity: caveat emptor. Endocrine Practice. 2008 Dec;14(9):1188-90. PMID: 19158058.

160. Taskapan H, Vieth R, Oreopoulos DG. Unusually prolonged vitamin D intoxication after discontinuation of vitamin D: possible role of primary hyperparathyroidism. International Urology & Nephrology. 2008;40(3):801-5. PMID: 18528779.

161. Abbas S, Linseisen J, Slanger T, et al. Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer--results of a large case-control study. Carcinogenesis. 2008 Jan;29(1):93-9. PMID: 17974532.

162. Bjelakovic G, Gluud Lise L, Nikolova D, et al. Vitamin D supplementation for prevention of cancer in adults. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2008.

163. Das Jai K, Salam Rehana A, Lassi Zohra S, et al. Food fortification with calcium and vitamin D: impact on health outcomes. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2012.

164. Scragg Robert KR, Kenealy T, Bryant Linda Julia M, et al. Vitamin D for preventing cardiovascular disease. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2013.

165. Yakoob Mohammad Y, Bhutta Zulfiqar A. Vitamin D supplementation for preventing infections in children less than five years of age. Cochrane Database of Systematic Reviews: John Wiley & Sons, Ltd; 2010.

166. Steer PJ. Is vitamin D supplementation in pregnancy advisable? Lancet. 2013 Jun 22;381(9884):2143-5. PMID: 23518315.

167. Demir M, Uyan U, Melek M. The effects of vitamin d deficiency on atrial fibrillation. Clinical & Applied Thrombosis/Hemostasis. 2014 Jan;20(1):98-103. PMID: 22826443.

168. Zheng XE, Lipka S, Li T, et al. The relationship of vitamin D status, smoking, and colorectal adenoma: a retrospective study in an ethnically diverse community. Journal of Steroid Biochemistry & Molecular Biology. 2013 Jul;136:280-3. PMID: 23000288.

169. Yousef FM, Jacobs ET, Kang PT, et al. Vitamin D status and breast cancer in Saudi Arabian women: case-control study. American Journal of Clinical Nutrition. 2013 Jul;98(1):105-10. PMID: 23697705.

170. Wong YY, Flicker L, Yeap BB, et al. Is hypovitaminosis D associated with abdominal aortic aneurysm, and is there a dose-response relationship? European Journal of Vascular & Endovascular Surgery. 2013 Jun;45(6):657-64. PMID: 23602862.

171. Wang LF, Lee CH, Chien CY, et al. Serum 25-hydroxyvitamin D levels are lower in chronic rhinosinusitis with nasal polyposis and are correlated with disease severity in Taiwanese patients. American Journal of Rhinology & Allergy. 2013 Nov;27(6):162-5. PMID: 24274207.

172. Vatanparast H, Nisbet C, Gushulak B. Vitamin D insufficiency and bone mineral status in a population of newcomer children in Canada. Nutrients. 2013 May;5(5):1561-72. PMID: 23673607.

173. Ullah MI, Koch CA, Tamanna S, et al. Vitamin d deficiency and the risk of preeclampsia and eclampsia in bangladesh. Hormone & Metabolic Research. 2013 Sep;45(9):682-7. PMID: 23733167.

174. Sy AM, Bautista JE. Association between serum vitamin D levels and colonic carcinomatous polyps. Journal of Gastrointestinal Cancer. 2013 Dec;44(4):481-5. PMID: 23925636.

175. Samochocki Z, Bogaczewicz J, Jeziorkowska R, et al. Vitamin D effects in atopic dermatitis. Journal of the American Academy of Dermatology. 2013 Aug;69(2):238-44. PMID: 23643343.

176. Remmelts HH, Spoorenberg SM, Oosterheert JJ, et al. The role of vitamin D supplementation in the risk of developing pneumonia: three independent case-control studies. Thorax. 2013 Nov;68(11):990-6. PMID: 23892991.

177. Ramly M, Moy FM, Pendek R, et al. Study protocol: the effect of vitamin D supplements on cardiometabolic risk factors among urban premenopausal women in a tropical country—a randomized controlled trial. BMC Public Health. 2013;13:416. PMID: 23631804.

178. Quraishi SA, Bittner EA, Christopher KB, et al. Vitamin d status and community-acquired pneumonia: results from the third national health and nutrition examination survey. PLoS ONE [Electronic Resource]. 2013;8(11):e81120. PMID: 24260547.

179. Pludowski P, Holick MF, Pilz S, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. Autoimmunity Reviews. 2013 Aug;12(10):976-89. PMID: 23542507.

180. O'Connell K, Kelly S, Kinsella K, et al. Dose-related effects of vitamin D on immune responses in patients with clinically isolated syndrome and healthy control participants: study protocol for an exploratory randomized double- blind placebo-controlled trial. Trials [Electronic Resource]. 2013;14(1):272. PMID: 23981773.

181. Malafarina V, Uriz-Otano F, Gil-Guerrero L, et al. Study protocol: High-protein nutritional intervention based on beta-hydroxy-beta-methylbutirate, vitamin D3 and calcium on obese and lean aged patients with hip fractures and sarcopenia. The HIPERPROT-GER study. Maturitas. 2013 Oct;76(2):123-8. PMID: 23891440.

182. Lumachi F, Camozzi V, Doretto P, et al. Circulating PTH, Vitamin D and IGF-I levels in relation to bone mineral density in elderly women. In Vivo. 2013 May-Jun;27(3):415-8. PMID: 23606700.

183. Jelsma JG, van Poppel MN, Galjaard S, et al. DALI: Vitamin D and lifestyle intervention for gestational diabetes mellitus (GDM) prevention: an European multicentre, randomised trial—study protocol. BMC Pregnancy & Childbirth. 2013;13:142. PMID: 23829946.

184. Jacobsen R, Abrahamsen B, Bauerek M, et al. The influence of early exposure to vitamin D for development of diseases later in life. BMC Public Health. 2013;13:515. PMID: 23714352.

185. Gergen PJ, Teach SJ, Mitchell HE, et al. Lack of a relation between serum 25-hydroxyvitamin D concentrations and asthma in adolescents. American Journal of Clinical Nutrition. 2013 Jun;97(6):1228-34. PMID: 23595876.

186. Cunningham E. Are there evidence-based dietary interventions for multiple sclerosis? Journal of the Academy of Nutrition & Dietetics. 2013 Jul;113(7):1004. PMID: 23790414.

187. Cashman KD, Kiely M. EURRECA-Estimating vitamin D requirements for deriving dietary reference values. Critical Reviews in Food Science & Nutrition. 2013;53(10):1097-109. PMID: 23952090.

188. Brondum-Jacobsen P, Benn M, Tybjaerg-Hansen A, et al. 25-Hydroxyvitamin D concentrations and risk of venous thromboembolism in the general population with 18,791 participants. Journal of Thrombosis & Haemostasis. 2013 Mar;11(3):423-31. PMID: 23279309.

189. Barker T, Henriksen VT, Martins TB, et al. Higher serum 25-hydroxyvitamin D concentrations associate with a faster recovery of skeletal muscle strength after muscular injury. Nutrients. 2013;5(4):1253-75. PMID: 23595134.

190. Aronsson CA, Vehik K, Yang J, et al. Use of dietary supplements in pregnant women in relation to sociodemographic factors—a report from The Environmental Determinants of Diabetes in the Young (TEDDY) study. Public Health Nutrition. 2013 Aug;16(8):1390-402. PMID: 23452986.

191. Chao YS, Brunel L, Faris P, et al. The importance of dose, frequency and duration of vitamin D supplementation for plasma 25-hydroxyvitamin D. Nutrients. 2013 Oct;5(10):4067-78. PMID: 24152747.

Co-morbidities Not of Interest—N=116

1. Agborsangaya CB, Lehtinen T, Toriola AT, et al. Association between Epstein-Barr virus infection and risk for development of pregnancy-associated breast cancer: joint effect with vitamin D? European Journal of Cancer. 2011 Jan;47(1):116-20. PMID: 20691583.

2. Agborsangaya CB, Surcel H-M, Toriola AT, et al. Serum 25-hydroxyvitamin D at pregnancy and risk of breast cancer in a prospective study. European Journal of Cancer. 2010 Feb;46(3):467-70. PMID: 20022237.

3. Aivo J, Lindsrom BM, Soilu-Hanninen M. A Randomised, Double-Blind, Placebo-Controlled Trial with Vitamin D3 in MS: Subgroup Analysis of Patients with Baseline Disease Activity Despite Interferon Treatment. Multiple Sclerosis International. 2012;2012:802796. PMID: 22919492.

4. Amestejani M, Salehi BS, Vasigh M, et al. Vitamin D supplementation in the treatment of atopic dermatitis: a clinical trial study. Journal of Drugs in Dermatology: JDD. 2012 Mar;11(3):327-30. PMID: 22395583.

5. Amir E, Cecchini RS, Ganz PA, et al. 25-Hydroxy vitamin-D, obesity, and associated variables as predictors of breast cancer risk and tamoxifen benefit in NSABP-P1. Breast Cancer Research & Treatment. 2012 Jun;133(3):1077-88. PMID: 22415479.

6. Bacon CJ, Gamble GD, Horne AM, et al. High-dose oral vitamin D3 supplementation in the elderly. Osteoporosis International. 2009 Aug;20(8):1407-15. PMID: 19101755.

7. Banajeh SM. Nutritional rickets and vitamin D deficiency—association with the outcomes of childhood very severe pneumonia: a prospective cohort study. Pediatric Pulmonology. 2009 Dec;44(12):1207-15. PMID: 19911367.

8. Batchelor F, Hill K, Mackintosh S, et al. What works in falls prevention after stroke?: a systematic review and meta-analysis. Stroke. 2010 Aug;41(8):1715-22. PMID: 20616328.

9. Center JR, Bliuc D, Nguyen ND, et al. Osteoporosis medication and reduced mortality risk in elderly women and men. Journal of Clinical Endocrinology & Metabolism. 2011 Apr;96(4):1006-14. PMID: 21289270.

10. Davison BJ, Wiens K, Cushing M. Promoting calcium and vitamin D intake to reduce the risk of osteoporosis in men on androgen deprivation therapy for recurrent prostate cancer. Supportive Care in Cancer. 2012 Oct;20(10):2287-94. PMID: 22138848.

11. Dukas L, Schacht E, Runge M, et al. Effect of a six-month therapy with alfacalcidol on muscle power and balance and the number of fallers and falls. Arzneimittel-Forschung. 2010;60(8):519-25. PMID: 20863009.

12. Eftekhari MH, Akbarzadeh M, Dabbaghmanesh MH, et al. Impact of treatment with oral calcitriol on glucose indices in type 2 diabetes mellitus patients. Asia Pacific Journal of Clinical Nutrition. 2011;20(4):521-6. PMID: 22094836.

13. Gaal J, Lakos G, Szodoray P, et al. Immunological and clinical effects of alphacalcidol in patients with psoriatic arthropathy: results of an open, follow-up pilot study. Acta Dermato-Venereologica. 2009;89(2):140-4. PMID: 19325997.

14. Gabbay MAL, Sato MN, Finazzo C, et al. Effect of cholecalciferol as adjunctive therapy with insulin on protective immunologic profile and decline of residual-cell function in new-onset type 1 diabetes mellitus. Archives of Pediatrics & Adolescent Medicine. 2012 Jul 1;166(7):601-7. PMID: 22751874.

15. Garcia MN, Hildebolt CF, Miley DD, et al. One-year effects of vitamin D and calcium supplementation on chronic periodontitis. Journal of Periodontology. 2011 Jan;82(1):25-32. PMID: 20809866.

16. Gugatschka M, Kiesler K, Obermayer-Pietsch B, et al. Vitamin D status is associated with disease-free survival and overall survival time in patients with squamous cell carcinoma of the upper aerodigestive tract. European Archives of Oto-Rhino-Laryngology. 2011 Aug;268(8):1201-4. PMID: 21221617.

17. Hanson C, Armas L, Lyden E, et al. Vitamin D status and associations in newborn formula-fed infants during initial hospitalization. Journal of the American Dietetic Association. 2011 Dec;111(12):1836-43. PMID: 22117659.

18. Hara S, Kishimoto KN, Okuno H, et al. Effects of alfacalcidol on back extensor strength gained through back extensor exercise in postmenopausal women with osteoporosis. American Journal of Physical Medicine & Rehabilitation. 2013 Feb;92(2):101-10. PMID: 23044701.

19. Harris SS, Pittas AG, Palermo NJ. A randomized, placebo-controlled trial of vitamin D supplementation to improve glycaemia in overweight and obese African Americans. Diabetes, Obesity & Metabolism. 2012 Sep;14(9):789-94. PMID: 22486948.

20. Helou J, Moutran R, Maatouk I, et al. Raynaud's phenomenon and vitamin D. Rheumatology International. 2013 Mar;33(3):751-5. PMID: 22580932.

21. Hiremath VP, Rao CB, Naik V, et al. Anti-inflammatory Effect of Vitamin D on Gingivitis: A Dose-Response Randomised Control Trial. Oral Health & Preventive Dentistry. 2013;11(1):61-9. PMID: 23507683.

22. Hoeck HC, Li B, Qvist P. Changes in 25-Hydroxyvitamin D3 to oral treatment with vitamin D3 in postmenopausal females with osteoporosis. Osteoporosis International. 2009 Aug;20(8):1329-35. PMID: 19083075.

23. Houston DK, Neiberg RH, Tooze JA, et al. Low 25-hydroxyvitamin D predicts the onset of mobility limitation and disability in community-dwelling older adults: the Health ABC Study. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2013 Feb;68(2):181-7. PMID: 22573914.

24. Houston DK, Tooze JA, Hausman DB, et al. Change in 25-hydroxyvitamin D and physical performance in older adults. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2011 Apr;66(4):430-6. PMID: 21325343.

25. Ishijima M, Sakamoto Y, Yamanaka M, et al. Minimum required vitamin D level for optimal increase in bone mineral density with alendronate treatment in osteoporotic women. Calcified Tissue International. 2009 Nov;85(5):398-404. PMID: 19795092.

26. Ito M, Nakamura T, Fukunaga M, et al. Effect of eldecalcitol, an active vitamin D analog, on hip structure and biomechanical properties: 3D assessment by clinical CT. Bone. 2011 Sep;49(3):328-34. PMID: 21605716.

27. Iwamoto J, Sato Y, Uzawa M, et al. Comparison of the effects of alendronate and alfacalcidol on hip bone mineral density and bone turnover in Japanese men having osteoporosis or osteopenia with clinical risk factors for fractures. Yonsei Medical Journal. 2009 Aug 31;50(4):474-81. PMID: 19718394.

28. Iwamoto N, Inaba Y, Kobayashi N, et al. A comparison of the effects of alendronate and alfacalcidol on bone mineral density around the femoral implant and in the lumbar spine after total hip arthroplasty. Journal of Bone & Joint Surgery—American Volume. 2011 Jul 6;93(13):1203-9. PMID: 21776573.

29. Janssen HCJP, Samson MM, Verhaar HJJ. Muscle strength and mobility in vitamin D-insufficient female geriatric patients: a randomized controlled trial on vitamin D and calcium supplementation. Aging-Clinical & Experimental Research. 2010 Feb;22(1):78-84. PMID: 20305368.

30. Javanbakht MH, Keshavarz SA, Djalali M, et al. Randomized controlled trial using vitamins E and D supplementation in atopic dermatitis. Journal of Dermatological Treatment. 2011 Jun;22(3):144-50. PMID: 20653487.

31. Joergensen C, Hovind P, Schmedes A, et al. Vitamin D levels, microvascular complications, and mortality in type 1 diabetes. Diabetes Care. 2011 May;34(5):1081-5. PMID: 21525501.

32. Judd SE, Raiser SN, Kumari M, et al. 1,25-dihydroxyvitamin D3 reduces systolic blood pressure in hypertensive adults: a pilot feasibility study. Journal of Steroid Biochemistry & Molecular Biology. 2010 Jul;121(1-2):445-7. PMID: 20420907.

33. Karaplis AC, Chouha F, Djandji M, et al. Vitamin D status and response to daily 400 IU vitamin D3 and weekly alendronate 70 mg in men and women with osteoporosis. Annals of Pharmacotherapy. 2011 May;45(5):561-8. PMID: 21521859.

34. Kluczynski MA, Wactawski-Wende J, Platek ME, et al. Changes in vitamin D supplement use and baseline plasma 25-hydroxyvitamin D concentration predict 5-y change in concentration in postmenopausal women. Journal of Nutrition. 2012 Sep;142(9):1705-12. PMID: 22833661.

35. Langdahl B, Binkley N, Bone H, et al. Odanacatib in the treatment of postmenopausal women with low bone mineral density: five years of continued therapy in a phase 2 study. Journal of Bone & Mineral Research. 2012 Nov;27(11):2251-8. PMID: 22777865.

36. Larsen T, Mose FH, Bech JN, et al. Effect of cholecalciferol supplementation during winter months in patients with hypertension: a randomized, placebo-controlled trial. American Journal of Hypertension. 2012 Nov;25(11):1215-22. PMID: 22854639.

37. Lasky-Su J, Lange N, Brehm JM, et al. Genome-wide association analysis of circulating vitamin D levels in children with asthma. Human Genetics. 2012 Sep;131(9):1495-505. PMID: 22673963.

38. Lerchbaum E, Pilz S, Boehm BO, et al. Combination of low free testosterone and low vitamin D predicts mortality in older men referred for coronary angiography. Clinical Endocrinology. 2012 Sep;77(3):475-83. PMID: 22356136.

39. Li M, Xing X-p, Zhang Z-l, et al. Infusion of ibandronate once every 3 months effectively decreases bone resorption markers and increases bone mineral density in Chinese postmenopausal osteoporotic women: a 1-year study. Journal of Bone & Mineral Metabolism. 2010 May;28(3):299-305. PMID: 19855926.

40. Li X, Liao L, Yan X, et al. Protective effects of 1-alpha-hydroxyvitamin D3 on residual beta-cell function in patients with adult-onset latent autoimmune diabetes (LADA). Diabetes/Metabolism Research Reviews. 2009 Jul;25(5):411-6. PMID: 19488999.

41. Lloyd BD, Williamson DA, Singh NA, et al. Recurrent and injurious falls in the year following hip fracture: a prospective study of incidence and risk factors from the Sarcopenia and Hip Fracture study. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2009 May;64(5):599-609. PMID: 19264957.

42. Majima T, Shimatsu A, Komatsu Y, et al. Effects of risedronate or alfacalcidol on bone mineral density, bone turnover, back pain, and fractures in Japanese men with primary osteoporosis: results of a two-year strict observational study. Journal of Bone & Mineral Metabolism. 2009;27(2):168-74. PMID: 19183836.

43. Matsumoto T, Ito M, Hayashi Y, et al. A new active vitamin D3 analog, eldecalcitol, prevents the risk of osteoporotic fractures--a randomized, active comparator, double-blind study. Bone. 2011 Oct;49(4):605-12. PMID: 21784190.

44. Mesliniene S, Ramrattan L, Giddings S, et al. Role of vitamin D in the onset, progression, and severity of multiple sclerosis. Endocrine Practice. 2013 Jan-Feb;19(1):129-36. PMID: 23186958.

45. Nagahama K, Kanayama M, Togawa D, et al. Does alendronate disturb the healing process of posterior lumbar interbody fusion? A prospective randomized trial. Journal of Neurosurgery Spine. 2011 Apr;14(4):500-7. PMID: 21275549.

46. Napoli N, Strollo R, Pitocco D, et al. Effect of calcitriol on bone turnover and osteocalcin in recent-onset type 1 diabetes. PLoS ONE [Electronic Resource]. 2013;8(2):e56488. PMID: 23437144.

47. Nazarian S, St Peter JV, Boston RC, et al. Vitamin D3 supplementation improves insulin sensitivity in subjects with impaired fasting glucose. Translational Research: The Journal Of Laboratory & Clinical Medicine. 2011 Nov;158(5):276-81. PMID: 22005267.

48. Neelemaat F, Bosmans JE, Thijs A, et al. Oral nutritional support in malnourished elderly decreases functional limitations with no extra costs. Clinical Nutrition. 2012 Apr;31(2):183-90. PMID: 22071290.

49. Neelemaat F, Lips P, Bosmans JE, et al. Short-term oral nutritional intervention with protein and vitamin D decreases falls in malnourished older adults. Journal of the American Geriatrics Society. 2012 Apr;60(4):691-9. PMID: 22316322.

50. Newton-Bishop JA, Beswick S, Randerson-Moor J, et al. Serum 25-hydroxyvitamin D3 levels are associated with breslow thickness at presentation and survival from melanoma. Journal of Clinical Oncology. 2009 Nov 10;27(32):5439-44. PMID: 19770375.

51. Neyens JC, van Haastregt JC, Dijcks BP, et al. Effectiveness and implementation aspects of interventions for preventing falls in elderly people in long-term care facilities: a systematic review of RCTs. Journal of the American Medical Directors Association. 2011 Jul;12(6):410-25. PMID: 21450201.

52. Nikooyeh B, Neyestani TR, Farvid M, et al. Daily consumption of vitamin D- or vitamin D + calcium-fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial. American Journal of Clinical Nutrition. 2011 Apr;93(4):764-71. PMID: 21289226.

53. Orimo H, Nakamura T, Fukunaga M, et al. Effects of alendronate plus alfacalcidol in osteoporosis patients with a high risk of fracture: the Japanese Osteoporosis Intervention Trial (JOINT)—02. Current Medical Research & Opinion. 2011 Jun;27(6):1273-84. PMID: 21554143.

54. Parikh S, Avorn J, Solomon DH. Pharmacological management of osteoporosis in nursing home populations: a systematic review. Journal of the American Geriatrics Society. 2009 Feb;57(2):327-34. PMID: 19207148.

55. Pfleiderer AG, Ahmad N, Draper MR, et al. The timing of calcium measurements in helping to predict temporary and permanent hypocalcaemia in patients having completion and total thyroidectomies. Annals of the Royal College of Surgeons of England. 2009 Mar;91(2):140-6. PMID: 19317937.

56. Pignotti GAP, Genaro PS, Pinheiro MM, et al. Is a lower dose of vitamin D supplementation enough to increase 25(OH)D status in a sunny country? European Journal of Nutrition. 2010 Aug;49(5):277-83. PMID: 19946776.

57. Pilz S, Dobnig H, Tomaschitz A, et al. Low 25-hydroxyvitamin D is associated with increased mortality in female nursing home residents. Journal of Clinical Endocrinology & Metabolism. 2012 Apr;97(4):E653-7. PMID: 22319037.

58. Premaor MO, Scalco R, da Silva MJS, et al. Secondary hyperparathyroidism is associated with increased risk of hospitalization or death in elderly adults living in a geriatric institution. Gerontology. 2009;55(4):405-10. PMID: 19571528.

59. Prieto-Alhambra D, Javaid MK, Servitja S, et al. Vitamin D threshold to prevent aromatase inhibitor-induced arthralgia: a prospective cohort study. Breast Cancer Research & Treatment. 2011 Feb;125(3):869-78. PMID: 20665105.

60. Punthakee Z, Bosch J, Dagenais G, et al. Design, history and results of the Thiazolidinedione Intervention with vitamin D Evaluation (TIDE) randomised controlled trial. Diabetologia. 2012 Jan;55(1):36-45. PMID: 22038523.

61. Quesada-Gomez JM, Muschitz C, Gomez-Reino J, et al. The effect of PTH(1-84) or strontium ranelate on bone formation markers in postmenopausal women with primary osteoporosis: results of a randomized, open-label clinical trial. Osteoporosis International. 2011 Sep;22(9):2529-37. PMID: 21052638.

62. Ralston SH, Binkley N, Boonen S, et al. Randomized trial of alendronate plus vitamin D3 versus standard care in osteoporotic postmenopausal women with vitamin D insufficiency. Calcified Tissue International. 2011 Jun;88(6):485-94. PMID: 21479913.

63. Rejnmark L, Vestergaard P, Brot C, et al. Increased fracture risk in normocalcemic postmenopausal women with high parathyroid hormone levels: a 16-year follow-up study. Calcified Tissue International. 2011 Mar;88(3):238-45. PMID: 21181400.

64. Ringe JD, Farahmand P, Faber H, et al. Sustained efficacy of risedronate in men with primary and secondary osteoporosis: results of a 2-year study. Rheumatology International. 2009 Jan;29(3):311-5. PMID: 18762944.

65. Ringe JD, Farahmand P, Schacht E. Alfacalcidol in men with osteoporosis: a prospective, observational, 2-year trial on 214 patients. Rheumatology International. 2013 Mar;33(3):637-43. PMID: 22527138.

66. Roschger P, Manjubala I, Zoeger N, et al. Bone material quality in transiliac bone biopsies of postmenopausal osteoporotic women after 3 years of strontium ranelate treatment. Journal of Bone & Mineral Research. 2010 Apr;25(4):891-900. PMID: 20437609.

67. Sahni S, Hannan MT, Blumberg J, et al. Protective effect of total carotenoid and lycopene intake on the risk of hip fracture: a 17-year follow-up from the Framingham Osteoporosis Study. Journal of Bone & Mineral Research. 2009 Jun;24(6):1086-94. PMID: 19138129.

68. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial.[Erratum appears in JAMA. 2010 Jun 16;303(23):2357]. JAMA. 2010 May 12;303(18):1815-22. PMID: 20460620.

69. Sato Y, Iwamoto J, Honda Y. An open-label trial comparing alendronate and alphacalcidol in reducing falls and hip fractures in disabled stroke patients. Journal of Stroke & Cerebrovascular Diseases. 2011 Jan-Feb;20(1):41-6. PMID: 20598577.

70. Schacht E, Ringe JD. Alfacalcidol improves muscle power, muscle function and balance in elderly patients with reduced bone mass. Rheumatology International. 2012 Jan;32(1):207-15. PMID: 20827552.

71. Schwartz JB. Effects of vitamin D supplementation in atorvastatin-treated patients: a new drug interaction with an unexpected consequence. Clinical Pharmacology & Therapeutics. 2009 Feb;85(2):198-203. PMID: 18754003.

72. Semba RD, Houston DK, Ferrucci L, et al. Low serum 25-hydroxyvitamin D concentrations are associated with greater all-cause mortality in older community-dwelling women. Nutrition Research. 2009 Aug;29(8):525-30. PMID: 19761886.

73. Shanafelt TD, Drake MT, Maurer MJ, et al. Vitamin D insufficiency and prognosis in chronic lymphocytic leukemia. Blood. 2011 Feb 3;117(5):1492-8. PMID: 21048153.

74. Shapses SA, Kendler DL, Robson R, et al. Effect of alendronate and vitamin D3 on fractional calcium absorption in a double-blind, randomized, placebo-controlled trial in postmenopausal osteoporotic women. Journal of Bone & Mineral Research. 2011 Aug;26(8):1836-44. PMID: 21448918.

75. Shiraki M, Saito H, Matsumoto T. Eldecalcitol normalizes bone turnover markers regardless of their pre-treatment levels. Current Medical Research & Opinion. 2012 Sep;28(9):1547-52. PMID: 22794117.

76. Sontag A, Krege JH. First fractures among postmenopausal women with osteoporosis. Journal of Bone & Mineral Metabolism. 2010 Jul;28(4):485-8. PMID: 20052602.

77. Soric MM, Renner ET, Smith SR. Effect of daily vitamin D supplementation on HbA1c in patients with uncontrolled type 2 diabetes mellitus: a pilot study. Journal Of Diabetes. 2012 Mar;4(1):104-5. PMID: 22018074.

78. Sridharan M, Cheung J, Moore AE, et al. Circulating fibroblast growth factor-23 increases following intermittent parathyroid hormone (1-34) in postmenopausal osteoporosis: association with biomarker of bone formation. Calcified Tissue International. 2010 Nov;87(5):398-405. PMID: 20838781.

79. Srinivas S, Feldman D. A phase II trial of calcitriol and naproxen in recurrent prostate cancer. Anticancer Research. 2009 Sep;29(9):3605-10. PMID: 19667155.

80. Tellioglu A, Basaran S, Guzel R, et al. Efficacy and safety of high dose intramuscular or oral cholecalciferol in vitamin D deficient/insufficient elderly. Maturitas. 2012 Aug;72(4):332-8. PMID: 22613271.

81. Tsai C-L, Delclos GL, Huang JS, et al. Age-related differences in asthma outcomes in the United States, 1988-2006. Annals of Allergy, Asthma, & Immunology. 2013 Apr;110(4):240-6.e1. PMID: 23535086.

82. Tse SM, Kelly HW, Litonjua AA, et al. Corticosteroid use and bone mineral accretion in children with asthma: effect modification by vitamin D. Journal of Allergy & Clinical Immunology. 2012 Jul;130(1):53-60.e4. PMID: 22608570.

83. Turner C, Dalton N, Inaoui R, et al. Effect of a 300 000-IU loading dose of ergocalciferol (Vitamin D2) on circulating 1,25(OH)2-vitamin D and fibroblast growth factor-23 (FGF-23) in vitamin D insufficiency. Journal of Clinical Endocrinology & Metabolism. 2013 Feb;98(2):550-6. PMID: 23284004.

84. Urashima M, Segawa T, Okazaki M, et al. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. American Journal of Clinical Nutrition. 2010 May;91(5):1255-60. PMID: 20219962.

85. Vacek JL, Vanga SR, Good M, et al. Vitamin D deficiency and supplementation and relation to cardiovascular health. American Journal of Cardiology. 2012 Feb 1;109(3):359-63. PMID: 22071212.

86. Vaidya A, Sun B, Larson C, et al. Vitamin D3 therapy corrects the tissue sensitivity to angiotensin ii akin to the action of a converting enzyme inhibitor in obese hypertensives: an interventional study. Journal of Clinical Endocrinology & Metabolism. 2012 Jul;97(7):2456-65. PMID: 22539586.

87. Walter M, Kaupper T, Adler K, et al. No effect of the 1alpha,25-dihydroxyvitamin D3 on beta-cell residual function and insulin requirement in adults with new-onset type 1 diabetes. Diabetes Care. 2010 Jul;33(7):1443-8. PMID: 20357369.

88. Waltman NL, Twiss JJ, Ott CD, et al. The effect of weight training on bone mineral density and bone turnover in postmenopausal breast cancer survivors with bone loss: a 24-month randomized controlled trial. Osteoporosis International. 2010 Aug;21(8):1361-9. PMID: 19802506.

89. Xia W-b, Zhang Z-l, Wang H-f, et al. The efficacy and safety of calcitriol and/or Caltrate D in elderly Chinese women with low bone mass. Zhongguo Yao Li Xue Bao/Acta Pharmacologica Sinica. 2009 Mar;30(3):372-8. PMID: 19262561.

90. Majak P, Olszowiec-Chlebna M, Smejda K, et al. Vitamin D supplementation in children may prevent asthma exacerbation triggered by acute respiratory infection. The Journal of allergy and clinical immunology; 2011. p. 1294-6.

91. Sidbury R, Sullivan AF, Thadhani RI, et al. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. The British journal of dermatology; 2008. p. 245-7.

92. Avenell A, MacLennan GS, Jenkinson DJ, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). The Journal of clinical endocrinology and metabolism; 2012. p. 614-22.

93. Zhang X, Li SW, Wu JF, et al. Effects of ipriflavone on postmenopausal syndrome and osteoporosis. Gynecological Endocrinology; 2010. p. 76-80.

94. Adami S, Isaia G, Luisetto G, et al. Osteoporosis treatment and fracture incidence: the ICARO longitudinal study. Osteoporosis International. 2008 Aug;19(8):1219-23. PMID: 18286217.

95. Buduneli N, Saygan BH, Karaduman U, et al. Calcium, vitamin D supplements with or without alendronate and supragingival calculus formation in osteoporotic women: a preliminary study. Expert Opinion on Pharmacotherapy. 2008 Aug;9(12):2015-20. PMID: 18671457.

96. Chen JS, Sambrook PN, March L, et al. Hypovitaminosis D and parathyroid hormone response in the elderly: effects on bone turnover and mortality. Clinical Endocrinology. 2008 Feb;68(2):290-8. PMID: 17854393.

97. Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. Archives of Internal Medicine. 2008 Jun 23;168(12):1340-9. PMID: 18574092.

98. Geller JL, Hu B, Reed S, et al. Increase in bone mass after correction of vitamin D insufficiency in bisphosphonate-treated patients. Endocrine Practice. 2008 Apr;14(3):293-7. PMID: 18463035.

99. Majima T, Komatsu Y, Shimatsu A, et al. Efficacy of combined treatment with raloxifene and alfacalcidol on bone density and biochemical markers of bone turnover in postmenopausal osteoporosis. Endocrine Journal. 2008 Mar;55(1):127-34. PMID: 18219181.

100. Pilz S, Dobnig H, Fischer JE, et al. Low vitamin d levels predict stroke in patients referred to coronary angiography. Stroke. 2008 Sep;39(9):2611-3. PMID: 18635847.

101. Pilz S, Dobnig H, Winklhofer-Roob B, et al. Low serum levels of 25-hydroxyvitamin D predict fatal cancer in patients referred to coronary angiography. Cancer Epidemiology, Biomarkers & Prevention. 2008 May;17(5):1228-33. PMID: 18463400.

102. Thornton J, Ashcroft D, O'Neill T, et al. A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management. Health Technology Assessment (Winchester, England). 2008 Mar;12(3):iii-ix, xi-xiv, 1-208. PMID: 18284894.

103. Witham MD, Dove FJ, Khan F, et al. Effects of Vitamin D supplementation on markers of vascular function after myocardial infarction--a randomised controlled trial. International Journal of Cardiology. 2013 Aug 10;167(3):745-9. PMID: 22459388.

104. Villasenor A, Ballard-Barbash R, Ambs A, et al. Associations of serum 25-hydroxyvitamin D with overall and breast cancer-specific mortality in a multiethnic cohort of breast cancer survivors. Cancer Causes & Control. 2013 Apr;24(4):759-67. PMID: 23361338.

105. Tohidi M, Bozorgmanesh M, Mohebi R, et al. Non-linear association between 25-hydroxyvitamin D and the incidence of type 2 diabetes: a community-based nested case-control study. Diabetic Medicine. 2013 Aug;30(8):934-8. PMID: 23560705.

106. Saliba W, Barnett-Griness O, Rennert G. The association between obesity and urinary tract infection. European Journal of Internal Medicine. 2013 Mar;24(2):127-31. PMID: 23199806.

107. Rees JR, Hendricks K, Barry EL, et al. Vitamin D3 supplementation and upper respiratory tract infections in a randomized, controlled trial. Clinical Infectious Diseases. 2013 Nov;57(10):1384-92. PMID: 24014734.

108. Mocanu V, Vieth R. Three-year follow-up of serum 25-hydroxyvitamin D, parathyroid hormone, and bone mineral density in nursing home residents who had received 12months of daily bread fortification with 125mug of vitamin D3. Nutrition Journal. 2013;12(1):137. PMID: 24120120.

109. Marchisio P, Consonni D, Baggi E, et al. Vitamin D supplementation reduces the risk of acute otitis media in otitis-prone children. Pediatric Infectious Disease Journal. 2013 Oct;32(10):1055-60. PMID: 23694840.

110. Lai L, Qian J, Yang Y, et al. Is the serum vitamin D level at the time of hospital-acquired acute kidney injury diagnosis associated with prognosis? PLoS ONE [Electronic Resource]. 2013;8(5):e64964. PMID: 23717679.

111. Chai W, Cooney RV, Franke AA, et al. Effects of calcium and vitamin D supplementation on blood pressure and serum lipids and carotenoids: a randomized, double-blind, placebo-controlled, clinical trial. Annals of Epidemiology. 2013 Sep;23(9):564-70. PMID: 23958407.

112. Carlson N, Mah R, Aburto M, et al. Hypovitaminosis d correction and high-sensitivity C-reactive protein levels in hypertensive adults. Permanente Journal. 2013;17(4):19-21. PMID: 24361015.

113. Bhattoa HP, Onyeka U, Kalina E, et al. Bone metabolism and the 10-year probability of hip fracture and a major osteoporotic fracture using the country-specific FRAX algorithm in men over 50 years of age with type 2 diabetes mellitus: a case-control study. Clinical Rheumatology. 2013 Aug;32(8):1161-7. PMID: 23588883.

114. Aziz M, Livak B, Burke-Miller J, et al. Vitamin D insufficiency may impair CD4 recovery among Women's Interagency HIV Study participants with advanced disease on HAART. AIDS. 2013 Feb 20;27(4):573-8. PMID: 23095316.

115. Amer M, Qayyum R. Relationship between 25-hydroxyvitamin D and all-cause and cardiovascular disease mortality. American Journal of Medicine. 2013 Jun;126(6):509-14. PMID: 23601272.

116. Alele JD, Luttrell LM, Hollis BW, et al. Relationship between vitamin D status and incidence of vascular events in the Veterans Affairs Diabetes Trial. Atherosclerosis. 2013 Jun;228(2):502-7. PMID: 23608249.

Interventions/Exposures/Predictors Not of Interest—N=111

1. Abbas S, Linseisen J, Rohrmann S, et al. Dietary intake of vitamin D and calcium and breast cancer risk in the European Prospective Investigation into Cancer and Nutrition. Nutrition & Cancer. 2013;65(2):178-87. PMID: 23441605.

2. Abbas S, Linseisen J, Rohrmann S, et al. Dietary intake of vitamin d and calcium and breast cancer risk in the European prospective investigation into cancer and nutrition. Nutrition & Cancer. 2013 Feb;65(2):178-87. PMID: 23441605.

3. Agarwal R, Virmani D, Jaipal ML, et al. Vitamin d status of low birth weight infants in Delhi: a comparative study. Journal of Tropical Pediatrics. 2012 Dec;58(6):446-50. PMID: 22529320.

4. Aggarwal V, Seth A, Marwaha RK, et al. Management of nutritional rickets in Indian children: a randomized controlled trial. Journal of Tropical Pediatrics. 2013 Apr;59(2):127-33. PMID: 23104564.

5. Albanes D, Mondul AM, Yu K, et al. Serum 25-hydroxy vitamin D and prostate cancer risk in a large nested case-control study. Cancer Epidemiology, Biomarkers & Prevention. 2011 Sep;20(9):1850-60. PMID: 21784952.

6. Al-Daghri NM, Alkharfy KM, Al-Othman A, et al. Effect of non-pharmacologic vitamin D status correction on circulating bone markers in healthy overweight and obese Saudis. Molecules. 2013;18(9):10671-80. PMID: 24002141.

7. Alekel DL, Van Loan MD, Koehler KJ, et al. The soy isoflavones for reducing bone loss (SIRBL) study: a 3-y randomized controlled trial in postmenopausal women. American Journal of Clinical Nutrition. 2010 Jan;91(1):218-30. PMID: 19906801.

8. Ananthakrishnan AN, Khalili H, Higuchi LM, et al. Higher predicted vitamin D status is associated with reduced risk of Crohn's disease. Gastroenterology. 2012 Mar;142(3):482-9. PMID: 22155183.

9. Antoniucci DM, Vittinghoff E, Palermo L, et al. Vitamin D insufficiency does not affect response of bone mineral density to alendronate. Osteoporosis International. 2009 Jul;20(7):1259-66. PMID: 19043656.

10. Avenell A, MacLennan GS, Jenkinson DJ, et al. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). Journal of Clinical Endocrinology & Metabolism. 2012 Feb;97(2):614-22. PMID: 22112804.

11. Bao Y, Ng K, Wolpin BM, et al. Predicted vitamin D status and pancreatic cancer risk in two prospective cohort studies. British Journal of Cancer. 2010 Apr 27;102(9):1422-7. PMID: 20389298.

12. Benetou V, Orfanos P, Zylis D, et al. Diet and hip fractures among elderly Europeans in the EPIC cohort. European Journal of Clinical Nutrition. 2011 Jan;65(1):132-9. PMID: 20948558.

13. Berggren M, Stenvall M, Olofsson B, et al. Evaluation of a fall-prevention program in older people after femoral neck fracture: a one-year follow-up. Osteoporosis International. 2008 Jun;19(6):801-9. PMID: 18030411.

14. Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Additive benefit of higher testosterone levels and vitamin D plus calcium supplementation in regard to fall risk reduction among older men and women. Osteoporosis International. 2008 Sep;19(9):1307-14. PMID: 18351428.

15. Cauley JA, Chlebowski RT, Wactawski-Wende J, et al. Calcium plus vitamin D supplementation and health outcomes five years after active intervention ended: the Women's Health Initiative. Journal of Women's Health. 2013 Nov;22(11):915-29. PMID: 24131320.

16. Costenbader KH, Feskanich D, Holmes M, et al. Vitamin D intake and risks of systemic lupus erythematosus and rheumatoid arthritis in women. Annals of the Rheumatic Diseases. 2008 Apr;67(4):530-5. PMID: 17666449.

17. Davidson MB, Duran P, Lee ML, et al. High-dose vitamin D supplementation in people with prediabetes and hypovitaminosis D. Diabetes Care. 2013 Feb;36(2):260-6. PMID: 23033239.

18. Edvardsen K, Veierod MB, Brustad M, et al. Vitamin D-effective solar UV radiation, dietary vitamin D and breast cancer risk. International Journal of Cancer. 2011 Mar 15;128(6):1425-33. PMID: 20473950.

19. Engel P, Fagherazzi G, Mesrine S, et al. Joint effects of dietary vitamin D and sun exposure on breast cancer risk: results from the French E3N cohort. Cancer Epidemiology, Biomarkers & Prevention. 2011 Jan;20(1):187-98. PMID: 21127286.

20. Erkkola M, Kaila M, Nwaru BI, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. Clinical & Experimental Allergy. 2009 Jun;39(6):875-82. PMID: 19522996.

21. Evans RK, Antczak AJ, Lester M, et al. Effects of a 4-month recruit training program on markers of bone metabolism. Medicine & Science in Sports & Exercise. 2008 Nov;40(11 Suppl):S660-70. PMID: 18849868.

22. Fan C, Nieto FJ, Bautista LE, et al. Vitamin D intake and cardiovascular mortality in the NHANES I epidemiological follow-up study cohort. Journal of Dietary Supplements. 2012 Jun;9(2):79-89. PMID: 22607643.

23. Farhanghi MA, Mahboob S, Ostadrahimi A. Obesity induced magnesium deficiency can be treated by vitamin D supplementation. JPMA—Journal of the Pakistan Medical Association. 2009 Apr;59(4):258-61. PMID: 19402296.

24. Felsenberg D, Bock O, Borst H, et al. Additive impact of alfacalcidol on bone mineral density and bone strength in alendronate treated postmenopausal women with reduced bone mass. Journal of Musculoskeletal Neuronal Interactions. 2011 Mar;11(1):34-45. PMID: 21364273.

25. Fonollá J, López-Huertas E, Machado FJ, et al. Milk enriched with “healthy fatty acids” improves cardiovascular risk markers and nutritional status in human volunteers. Nutrition (Burbank, Los Angeles County, Calif.); 2009. p. 408-14.

26. Gaal J, Bender T, Varga J, et al. Overcoming resistance to bisphosphonates through the administration of alfacalcidol: results of a 1-year, open follow-up study. Rheumatology International. 2009 Nov;30(1):25-31. PMID: 19308412.

27. Ganry O, Lapotre-Ledoux B, Fardellone P, et al. Bone mass density, subsequent risk of colon cancer and survival in postmenopausal women. European Journal of Epidemiology. 2008;23(7):467-73. PMID: 18470627.

28. Gilbert R, Metcalfe C, Oliver SE, et al. Life course sun exposure and risk of prostate cancer: population-based nested case-control study and meta-analysis. International Journal of Cancer. 2009 Sep 15;125(6):1414-23. PMID: 19444909.

29. Gonzalez CA, Travier N, Lujan-Barroso L, et al. Dietary factors and in situ and invasive cervical cancer risk in the European prospective investigation into cancer and nutrition study. International Journal of Cancer. 2011 Jul 15;129(2):449-59. PMID: 20853322.

30. Gutin B, Stallmann-Jorgensen IS, Le AH, et al. Relations of diet and physical activity to bone mass and height in black and white adolescents. Pediatric Reports. 2011 Jun 16;3(2):e10. PMID: 21772947.

31. Hagstrom E, Ingelsson E, Sundstrom J, et al. Plasma parathyroid hormone and risk of congestive heart failure in the community. European Journal of Heart Failure. 2010 Nov;12(11):1186-92. PMID: 20797986.

32. Harris HR, Chavarro JE, Malspeis S, et al. Dairy-food, calcium, magnesium, and vitamin D intake and endometriosis: a prospective cohort study. American Journal of Epidemiology. 2013 Mar 1;177(5):420-30. PMID: 23380045.

33. Haugen M, Brantsaeter AL, Trogstad L, et al. Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. Epidemiology. 2009 Sep;20(5):720-6. PMID: 19451820.

34. Hettiarachchi M, Lekamwasam S, Liyanage C. Long-term cereal-based nutritional supplementation improved the total spine bone mineral density amongst Sri Lankan preschool children: a randomized controlled study. Journal of Pediatric Endocrinology. 2010 Jun;23(6):555-63. PMID: 20662329.

35. Hinton PS, Rector RS, Donnelly JE, et al. Total body bone mineral content and density during weight loss and maintenance on a low- or recommended-dairy weight-maintenance diet in obese men and women. European Journal of Clinical Nutrition. 2010 Apr;64(4):392-9. PMID: 20068585.

36. Hiraki LT, Munger KL, Costenbader KH, et al. Dietary intake of vitamin D during adolescence and risk of adult-onset systemic lupus erythematosus and rheumatoid arthritis. Arthritis care & research. 2012 Dec;64(12):1829-36. PMID: 22744978.

37. Holecki M, Zahorska-Markiewicz B, Wiecek A, et al. Influence of calcium and vitamin D supplementation on weight and fat loss in obese women. Obesity facts; 2008. p. 274-9.

38. Holm L, Olesen JL, Matsumoto K, et al. Protein-containing nutrient supplementation following strength training enhances the effect on muscle mass, strength, and bone formation in postmenopausal women. Journal of Applied Physiology. 2008 Jul;105(1):274-81. PMID: 18467544.

39. Horn LV, Tian L, Neuhouser ML, et al. Dietary patterns are associated with disease risk among participants in the Women's Health Initiative Observational Study. Journal of Nutrition. 2012 Feb;142(2):284-91. PMID: 22190026.

40. Hypponen E, Fararouei M, Sovio U, et al. High-dose vitamin D supplements are not associated with linear growth in a large Finnish cohort. Journal of Nutrition. 2011 May;141(5):843-8. PMID: 21430256.

41. Ishihara J, Inoue M, Iwasaki M, et al. Dietary calcium, vitamin D, and the risk of colorectal cancer. American Journal of Clinical Nutrition. 2008 Dec;88(6):1576-83. PMID: 19064518.

42. Itariu BK, Zeyda M, Leitner L, et al. Treatment with n-3 polyunsaturated fatty acids overcomes the inverse association of vitamin D deficiency with inflammation in severely obese patients: a randomized controlled trial. PLoS ONE [Electronic Resource]. 2013;8(1):e54634. PMID: 23372745.

43. Jacobs ET, Hibler EA, Lance P, et al. Association between circulating concentrations of 25(OH)D and colorectal adenoma: a pooled analysis. International Journal of Cancer. 2013 Dec 15;133(12):2980-8. PMID: 23754630.

44. Jeon H, Lee S, Kim TE, et al. Pharmacokinetics and tolerability of probucol after multiple oral administrations in healthy volunteers. International journal of clinical pharmacology and therapeutics; 2011. p. 688-95.

45. Karami S, Andreotti G, Koutros S, et al. Pesticide exposure and inherited variants in vitamin d pathway genes in relation to prostate cancer. Cancer Epidemiology, Biomarkers & Prevention. 2013 Sep;22(9):1557-66. PMID: 23833127.

46. Kiehn KA, Mahoney J, Jones AN, et al. Vitamin D supplement intake in elderly fallers. Journal of the American Geriatrics Society; 2009. p. 176-7.

47. Kim M-J, Na B, No S-J, et al. Nutritional status of vitamin D and the effect of vitamin D supplementation in Korean breast-fed infants. Journal of Korean Medical Science. 2010 Jan;25(1):83-9. PMID: 20052352.

48. Kirii K, Mizoue T, Iso H, et al. Calcium, vitamin D and dairy intake in relation to type 2 diabetes risk in a Japanese cohort. Diabetologia. 2009 Dec;52(12):2542-50. PMID: 19823801.

49. Kojima G, Bell C, Abbott RD, et al. Low dietary vitamin D predicts 34-year incident stroke: the Honolulu Heart Program. Stroke. 2012 Aug;43(8):2163-7. PMID: 22627988.

50. Kota BP, Abdul MIM, Allen JD, et al. Effect of vitamin D3 supplementation on the pharmacokinetics of digoxin--a pilot study. Fundamental & Clinical Pharmacology. 2012 Aug;26(4):543-8. PMID: 21477267.

51. Kristal AR, Arnold KB, Schenk JM, et al. Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. American Journal of Epidemiology. 2008 Apr 15;167(8):925-34. PMID: 18263602.

52. Kruger MC, Schollum LM, Kuhn-Sherlock B, et al. The effect of a fortified milk drink on vitamin D status and bone turnover in post-menopausal women from South East Asia. Bone; 2010. p. 759-67.

53. Kuper H, Yang L, Sandin S, et al. Prospective study of solar exposure, dietary vitamin D intake, and risk of breast cancer among middle-aged women. Cancer Epidemiology, Biomarkers & Prevention. 2009 Sep;18(9):2558-61. PMID: 19690185.

54. Lappe J, Kunz I, Bendik I, et al. Effect of a combination of genistein, polyunsaturated fatty acids and vitamins D3 and K1 on bone mineral density in postmenopausal women: a randomized, placebo-controlled, double-blind pilot study. European Journal of Nutrition. 2013 Feb;52(1):203-15. PMID: 22302614.

55. Leventis P, Kiely PDW. The tolerability and biochemical effects of high-dose bolus vitamin D2 and D3 supplementation in patients with vitamin D insufficiency. Scandinavian Journal of Rheumatology. 2009 Mar-Apr;38(2):149-53. PMID: 18991184.

56. Lindelof B, Krynitz B, Ayoubi S, et al. Previous extensive sun exposure and subsequent vitamin D production in patients with basal cell carcinoma of the skin, has no protective effect on internal cancers. European Journal of Cancer. 2012 May;48(8):1154-8. PMID: 21788128.

57. Liu E, McKeown NM, Pittas AG, et al. Predicted 25-hydroxyvitamin D score and change in fasting plasma glucose in the Framingham offspring study. European Journal of Clinical Nutrition. 2012 Jan;66(1):139-41. PMID: 22009071.

58. Liu JJ, Bertrand KA, Karageorgi S, et al. Prospective analysis of vitamin D and endometrial cancer risk. Annals of Oncology. 2013 Mar;24(3):687-92. PMID: 23136228.

59. Lucey AJ, Paschos GK, Cashman KD, et al. Influence of moderate energy restriction and seafood consumption on bone turnover in overweight young adults. The American journal of clinical nutrition; 2008. p. 1045-52.

60. Maki KC, Rubin MR, Wong LG, et al. Effects of vitamin D supplementation on 25-hydroxyvitamin D, high-density lipoprotein cholesterol, and other cardiovascular disease risk markers in subjects with elevated waist circumference. International Journal of Food Sciences & Nutrition. 2011 Jun;62(4):318-27. PMID: 21250901.

61. Martin-Bautista E, Muñoz-Torres M, Fonolla J, et al. Improvement of bone formation biomarkers after 1-year consumption with milk fortified with eicosapentaenoic acid, docosahexaenoic acid, oleic acid, and selected vitamins. Nutrition research (New York, N.Y.); 2010. p. 320-6.

62. Mason C, Xiao L, Imayama I, et al. Effects of weight loss on serum vitamin D in postmenopausal women. The American journal of clinical nutrition; 2011. p. 95-103.

63. Mason C, Xiao L, Imayama I, et al. Influence of diet, exercise, and serum vitamin d on sarcopenia in postmenopausal women. Medicine & Science in Sports & Exercise. 2013 Apr;45(4):607-14. PMID: 23190588.

64. Matsumoto T, Takano T, Yamakido S, et al. Comparison of the effects of eldecalcitol and alfacalcidol on bone and calcium metabolism. Journal of Steroid Biochemistry & Molecular Biology. 2010 Jul;121(1-2):261-4. PMID: 20298784.

65. McLean RR, Jacques PF, Selhub J, et al. Plasma B vitamins, homocysteine, and their relation with bone loss and hip fracture in elderly men and women. Journal of Clinical Endocrinology & Metabolism. 2008 Jun;93(6):2206-12. PMID: 18364381.

66. Merlino LA, Curtis J, Mikuls TR, et al. Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. Arthritis Rheum. 2004 Jan;50(1):72-7. PMID: 14730601.

67. Moran DS, Heled Y, Arbel Y, et al. Dietary intake and stress fractures among elite male combat recruits. Journal of the International Society of Sports Nutrition. 2012;9(1):6. PMID: 22413851.

68. Munger KL, Chitnis T, Frazier AL, et al. Dietary intake of vitamin D during adolescence and risk of multiple sclerosis. Journal of Neurology. 2011 Mar;258(3):479-85. PMID: 20945071.

69. Munger KL, Levin LI, O'Reilly EJ, et al. Anti-Epstein-Barr virus antibodies as serological markers of multiple sclerosis: a prospective study among United States military personnel. Multiple Sclerosis. 2011 Oct;17(10):1185-93. PMID: 21685232.

70. Neelemaat F, Bosmans JE, Thijs A, et al. Post-discharge nutritional support in malnourished elderly individuals improves functional limitations. Journal of the American Medical Directors Association. 2011 May;12(4):295-301. PMID: 21527171.

71. Neuhouser ML, Wassertheil-Smoller S, Thomson C, et al. Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. Archives of Internal Medicine. 2009 Feb 9;169(3):294-304. PMID: 19204221.

72. Nieves JW, Melsop K, Curtis M, et al. Nutritional factors that influence change in bone density and stress fracture risk among young female cross-country runners. Pm & R. 2010 Aug;2(8):740-50; quiz 94. PMID: 20709302.

73. O'Connor DL, Khan S, Weishuhn K, et al. Growth and nutrient intakes of human milk-fed preterm infants provided with extra energy and nutrients after hospital discharge. Pediatrics; 2008. p. 766-76.

74. Palacios S, Rojo IA, Cancelo MJ, et al. Women's perception of the efficacy of a soy extract with probiotic: the M3 study. Gynecological Endocrinology. 2008 Apr;24(4):178-83. PMID: 18382902.

75. Palvanen M, Kannus P, Piirtola M, et al. Effectiveness of the Chaos Falls Clinic in preventing falls and injuries of home-dwelling older adults: A randomised controlled trial. Injury. 2014 Jan;45(1):265-71. PMID: 23579066.

76. Pentti K, Tuppurainen MT, Honkanen R, et al. Use of calcium supplements and the risk of coronary heart disease in 52-62-year-old women: The Kuopio Osteoporosis Risk Factor and Prevention Study. Maturitas. 2009 May 20;63(1):73-8. PMID: 19394167.

77. Porojnicu AC, Bruland OS, Aksnes L, et al. Sun beds and cod liver oil as vitamin D sources. Journal of photochemistry and photobiology. B, Biology; 2008. p. 125-31.

78. Prelack K, Dwyer J, Ziegler P, et al. Bone mineral density in elite adolescent female figure skaters. Journal of the International Society of Sports Nutrition. 2012;9(1):57. PMID: 23270306.

79. Prescott J, Bertrand KA, Poole EM, et al. Surrogates of long-term vitamin d exposure and ovarian cancer risk in two prospective cohort studies. Cancer. 2013;5(4):1577-600. PMID: 24351671.

80. Puri S, Marwaha RK, Agarwal N, et al. Vitamin D status of apparently healthy schoolgirls from two different socioeconomic strata in Delhi: relation to nutrition and lifestyle. British Journal of Nutrition. 2008 Apr;99(4):876-82. PMID: 17903343.

81. Rajakumar K, Fernstrom JD, Holick MF, et al. Vitamin D status and response to Vitamin D(3) in obese vs. non-obese African American children. Obesity. 2008 Jan;16(1):90-5. PMID: 18223618.

82. Rautiainen S, Akesson A, Levitan EB, et al. Multivitamin use and the risk of myocardial infarction: a population-based cohort of Swedish women.[Erratum appears in Am J Clin Nutr. 2011 Mar;93(3):674]. American Journal of Clinical Nutrition. 2010 Nov;92(5):1251-6. PMID: 20861174.

83. Rejnmark L, Vestergaard P, Heickendorff L, et al. Simvastatin does not affect vitamin d status, but low vitamin d levels are associated with dyslipidemia: results from a randomised, controlled trial. International Journal of Endocrinology Print. 2010;2010:957174. PMID: 20016680.

84. Rohan TE, Negassa A, Caan B, et al. Low-fat dietary pattern and risk of benign proliferative breast disease: a randomized, controlled dietary modification trial. Cancer Prevention Research. 2008 Sep;1(4):275-84. PMID: 19138971.

85. Romeo J, Wärnberg J, García-Mármol E, et al. Daily consumption of milk enriched with fish oil, oleic acid, minerals and vitamins reduces cell adhesion molecules in healthy children. Nutrition, metabolism, and cardiovascular diseases : NMCD; 2011. p. 113-20.

86. Sai AJ, Gallagher JC, Smith LM, et al. Fall predictors in the community dwelling elderly: a cross sectional and prospective cohort study. Journal of Musculoskeletal Neuronal Interactions. 2010 Jun;10(2):142-50. PMID: 20516631.

87. Samelson EJ, Booth SL, Fox CS, et al. Calcium intake is not associated with increased coronary artery calcification: the Framingham Study. American Journal of Clinical Nutrition. 2012 Dec;96(6):1274-80. PMID: 23134889.

88. Scheinfeld NS. Calcipotriene 0.005% and betamethasone dipropionate 0.064% combination topical suspension (Taclonex Scalp). SKINmed. 2011 May-Jun;9(3):179-80. PMID: 21675498.

89. Scholl TO, Chen X. Vitamin D intake during pregnancy: association with maternal characteristics and infant birth weight. Early Human Development. 2009 Apr;85(4):231-4. PMID: 19008055.

90. Soares PAO, Kovacs C, Moreira P, et al. Is intake of vitamin D and calcium important for cardiovascular health in elderly obese patients? Obesity Surgery. 2012 Mar;22(3):437-44. PMID: 22246394.

91. Songpatanasilp T, Chailurkit L-O, Nichachotsalid A, et al. Combination of alfacalcidol with calcium can improve quadriceps muscle strength in elderly ambulatory Thai women who have hypovitaminosis D: a randomized controlled trial. Journal of the Medical Association of Thailand. 2009 Sep;92 Suppl5:S30-41. PMID: 19894330.

92. Sonneville KR, Gordon CM, Kocher MS, et al. Vitamin d, calcium, and dairy intakes and stress fractures among female adolescents. Archives of Pediatrics & Adolescent Medicine. 2012 Jul 1;166(7):595-600. PMID: 22393172.

93. Spector TD, Calomme MR, Anderson SH, et al. Choline-stabilized orthosilicic acid supplementation as an adjunct to calcium/vitamin D3 stimulates markers of bone formation in osteopenic females: a randomized, placebo-controlled trial. BMC musculoskeletal disorders; 2008. p. 85.

94. Stenova E, Steno B, Killinger Z, et al. Effect of long-term oral anticoagulant therapy on bone mineral density and bone turnover markers: a prospective 12 month study. Bratislavske Lekarske Listy. 2011;112(2):71-6. PMID: 21456505.

95. Su X, Colditz GA, Collins LC, et al. Adolescent intakes of vitamin D and calcium and incidence of proliferative benign breast disease. Breast Cancer Research & Treatment. 2012 Jul;134(2):783-91. PMID: 22622809.

96. Sun Q, Shi L, Rimm EB, et al. Vitamin D intake and risk of cardiovascular disease in US men and women. American Journal of Clinical Nutrition. 2011 Aug;94(2):534-42. PMID: 21653796.

97. Sverdlov AL, Ngo DTM, Chan WPA, et al. Determinants of aortic sclerosis progression: implications regarding impairment of nitric oxide signalling and potential therapeutics. European Heart Journal. 2012 Oct;33(19):2419-25. PMID: 22771677.

98. Takata Y, Shu X-O, Yang G, et al. Calcium intake and lung cancer risk among female nonsmokers: a report from the Shanghai Women's Health Study. Cancer Epidemiology, Biomarkers & Prevention. 2013 Jan;22(1):50-7. PMID: 23093548.

99. Tenta R, Moschonis G, Koutsilieris M, et al. Calcium and vitamin D supplementation through fortified dairy products counterbalances seasonal variations of bone metabolism indices: the Postmenopausal Health Study. European Journal of Nutrition. 2011 Aug;50(5):341-9. PMID: 21153900.

100. Thorp JM, Camargo CA, McGee PL, et al. Vitamin D status and recurrent preterm birth: a nested case-control study in high-risk women. BJOG: An International Journal of Obstetrics & Gynaecology. 2012 Dec;119(13):1617-23. PMID: 23078336.

101. van de Lagemaat M, Rotteveel J, Schaafsma A, et al. Higher vitamin D intake in preterm infants fed an isocaloric, protein- and mineral-enriched postdischarge formula is associated with increased bone accretion. Journal of Nutrition. 2013 Sep;143(9):1439-44. PMID: 23902955.

102. Vande Griend JP, Linnebur SA, Ruscin JM, et al. Vitamin D intervention by pharmacists in geriatric outpatients. Journal of the American Pharmacists Association: JAPhA. 2008 Jul-Aug;48(4):501-7. PMID: 18653426.

103. Vinceti M, Malagoli C, Fiorentini C, et al. Inverse association between dietary vitamin D and risk of cutaneous melanoma in a northern Italy population. Nutrition & Cancer. 2011;63(4):506-13. PMID: 21541899.

104. Watson PE, McDonald BW. The association of maternal diet and dietary supplement intake in pregnant New Zealand women with infant birthweight. European Journal of Clinical Nutrition. 2010 Feb;64(2):184-93. PMID: 19920847.

105. Weinstein SJ, Stolzenberg-Solomon RZ, Kopp W, et al. Impact of circulating vitamin D binding protein levels on the association between 25-hydroxyvitamin D and pancreatic cancer risk: a nested case-control study. Cancer Research. 2012 Mar 1;72(5):1190-8. PMID: 22232734.

106. Weinstein SJ, Yu K, Horst RL, et al. Serum 25-hydroxyvitamin D and risks of colon and rectal cancer in Finnish men. American Journal of Epidemiology. 2011 Mar 1;173(5):499-508. PMID: 21248311.

107. White KM, Bauer SJ, Hartz KK, et al. Changes in body composition with yogurt consumption during resistance training in women. International Journal of Sport Nutrition & Exercise Metabolism. 2009 Feb;19(1):18-33. PMID: 19403951.

108. Wilson RT, Wang J, Chinchilli V, et al. Fish, vitamin D, and flavonoids in relation to renal cell cancer among smokers. American Journal of Epidemiology. 2009 Sep 15;170(6):717-29. PMID: 19651663.

109. Zabihiyeganeh M, Jahed A, Nojomi M. Treatment of hypovitaminosis D with pharmacologic doses of cholecalciferol, oral vs intramuscular; an open labeled RCT. Clinical Endocrinology. 2013 Feb;78(2):210-6. PMID: 22882353.

110. Zhou W, Langsetmo L, Berger C, et al. Longitudinal changes in calcium and vitamin D intakes and relationship to bone mineral density in a prospective population-based study: the Canadian Multicentre Osteoporosis Study (CaMos). Journal of Musculoskeletal Neuronal Interactions. 2013 Dec;13(4):470-9. PMID: 24292617.

111. Zittermann A, Frisch S, Berthold HK, et al. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. American Journal of Clinical Nutrition. 2009 May;89(5):1321-7. PMID: 19321573.

Comparator/Placebo Not of Interest—N=36

1. Aguirre Castaneda R, Nader N, Weaver A, et al. Response to vitamin D3 supplementation in obese and non-obese Caucasian adolescents. Hormone research in pdiatrics. 2012;78(4):226-31. PMID: 23128469.

2. Allen AC, Kelly S, Basdeo SA, et al. A pilot study of the immunological effects of high-dose vitamin D in healthy volunteers. Multiple Sclerosis. 2012 Dec;18(12):1797-800. PMID: 22457344.

3. Back O, Blomquist HKS, Hernell O, et al. Does vitamin D intake during infancy promote the development of atopic allergy? Acta Dermato-Venereologica. 2009;89(1):28-32. PMID: 19197538.

4. Bischoff-Ferrari HA, Dawson-Hughes B, Stocklin E, et al. Oral supplementation with 25(OH)D3 versus vitamin D3: effects on 25(OH)D levels, lower extremity function, blood pressure, and markers of innate immunity. Journal of Bone & Mineral Research. 2012 Jan;27(1):160-9. PMID: 22028071.

5. Cipriani C, Romagnoli E, Scillitani A, et al. Effect of a single oral dose of 600,000 IU of cholecalciferol on serum calciotropic hormones in young subjects with vitamin D deficiency: a prospective intervention study. Journal of Clinical Endocrinology & Metabolism. 2010 Oct;95(10):4771-7. PMID: 20660032.

6. Coelho IMG, Andrade LDd, Saldanha L, et al. Bioavailability of vitamin D3 in non-oily capsules: the role of formulated compounds and implications for intermittent replacement. Arquivos Brasileiros de Endocrinologia e Metabologia. 2010 Mar;54(2):239-43. PMID: 20485915.

7. Colacurci N, De Franciscis P, Atlante M, et al. Endometrial, breast and liver safety of soy isoflavones plus Lactobacillus sporogenes in post-menopausal women. Gynecological Endocrinology. 2013 Mar;29(3):209-12. PMID: 23194023.

8. Colon-Emeric CS, Lyles KW, Su G, et al. Clinical risk factors for recurrent fracture after hip fracture: a prospective study. Calcified Tissue International. 2011 May;88(5):425-31. PMID: 21331567.

9. Dinizulu T, Griffin D, Carey J, et al. Vitamin D supplementation versus combined calcium and vitamin D in older female patients—an observational study. Journal of Nutrition, Health & Aging. 2011 Aug;15(8):605-8. PMID: 21968853.

10. Ekbote VH, Khadilkar AV, Chiplonkar SA, et al. A pilot randomized controlled trial of oral calcium and vitamin D supplementation using fortified laddoos in underprivileged Indian toddlers. European Journal of Clinical Nutrition. 2011 Apr;65(4):440-6. PMID: 21245882.

11. Gallo S, Phan A, Vanstone CA, et al. The change in plasma 25-hydroxyvitamin D did not differ between breast-fed infants that received a daily supplement of ergocalciferol or cholecalciferol for 3 months. Journal of Nutrition. 2013 Feb;143(2):148-53. PMID: 23256143.

12. Heaney RP, Recker RR, Grote J, et al. Vitamin D(3) is more potent than vitamin D(2) in humans. Journal of Clinical Endocrinology & Metabolism. 2011 Mar;96(3):E447-52. PMID: 21177785.

13. Herrmann W, Kirsch SH, Kruse V, et al. One year B and D vitamins supplementation improves metabolic bone markers. Clinical Chemistry & Laboratory Medicine. 2013 Mar 1;51(3):639-47. PMID: 23183751.

14. Holvik K, Madar AA, Meyer HE, et al. Changes in the vitamin D endocrine system and bone turnover after oral vitamin D3 supplementation in healthy adults: results of a randomised trial. BMC Endocrine Disorders. 2012;12:7. PMID: 22695105.

15. Husemoen LLN, Thuesen BH, Fenger M, et al. Serum 25(OH)D and type 2 diabetes association in a general population: a prospective study. Diabetes Care. 2012 Aug;35(8):1695-700. PMID: 22688545.

16. Kanellakis S, Moschonis G, Tenta R, et al. Changes in parameters of bone metabolism in postmenopausal women following a 12-month intervention period using dairy products enriched with calcium, vitamin D, and phylloquinone (vitamin K(1)) or menaquinone-7 (vitamin K (2)): the Postmenopausal Health Study II. Calcified Tissue International. 2012 Apr;90(4):251-62. PMID: 22392526.

17. Leaf DE, Korets R, Taylor EN, et al. Effect of vitamin D repletion on urinary calcium excretion among kidney stone formers. Clinical Journal of The American Society of Nephrology: CJASN. 2012 May;7(5):829-34. PMID: 22422535.

18. Logan VF, Gray AR, Peddie MC, et al. Long-term vitamin D3 supplementation is more effective than vitamin D2 in maintaining serum 25-hydroxyvitamin D status over the winter months. British Journal of Nutrition. 2013 Mar;109(6):1082-8. PMID: 23168298.

19. Marwaha RK, Tandon N, Agarwal N, et al. Impact of two regimens of vitamin D supplementation on calcium—vitamin D—PTH axis of schoolgirls of Delhi. Indian Pediatrics. 2010 Sep;47(9):761-9. PMID: 20308769.

20. Park CY, Hill KM, Elble AE, et al. Daily supplementation with 25 ug cholecalciferol does not increase calcium absorption or skeletal retention in adolescent girls with low serum 25-hydroxyvitamin D. Journal of Nutrition. 2010 Dec;140(12):2139-44. PMID: 20962148.

21. Pekkarinen T, Valimaki V-V, Aarum S, et al. The same annual dose of 292000 IU of vitamin D (cholecalciferol) on either daily or four monthly basis for elderly women: 1-year comparative study of the effects on serum 25(OH)D concentrations and renal function. Clinical Endocrinology. 2010 Apr;72(4):455-61. PMID: 19486025.

22. Pierce D, Hossack S, Poole L, et al. The effect of sevelamer carbonate and lanthanum carbonate on the pharmacokinetics of oral calcitriol. Nephrology Dialysis Transplantation. 2011 May;26(5):1615-21. PMID: 20921291.

23. Prietl B, Pilz S, Wolf M, et al. Vitamin D supplementation and regulatory T cells in apparently healthy subjects: vitamin D treatment for autoimmune diseases? Israel Medical Association Journal: Imaj. 2010 Mar;12(3):136-9. PMID: 20684175.

24. Raimundo FV, Faulhaber GAM, Menegatti PK, et al. Effect of High- versus Low-Fat Meal on Serum 25-Hydroxyvitamin D Levels after a Single Oral Dose of Vitamin D: A Single-Blind, Parallel, Randomized Trial. International Journal of Endocrinology Print. 2011;2011:809069. PMID: 22190928.

25. Roth DE, Al Mahmud A, Raqib R, et al. Pharmacokinetics of a single oral dose of vitamin D3 (70,000 IU) in pregnant and non-pregnant women. Nutrition Journal. 2012;11:114. PMID: 23268736.

26. Roth DE, Mahmud AA, Raqib R, et al. Pharmacokinetics of High-Dose Weekly Oral Vitamin D3 Supplementation during the Third Trimester of Pregnancy in Dhaka, Bangladesh. Nutrients. 2013;5(3):788-810. PMID: 23482056.

27. Russo S, Carlucci L, Cipriani C, et al. Metabolic changes following 500 ug monthly administration of calcidiol: a study in normal females. Calcified Tissue International. 2011 Sep;89(3):252-7. PMID: 21701937.

28. Steinberg FM, Murray MJ, Lewis RD, et al. Clinical outcomes of a 2-y soy isoflavone supplementation in menopausal women. American Journal of Clinical Nutrition. 2011 Feb;93(2):356-67. PMID: 21177797.

29. Thacher TD, Aliu O, Griffin IJ, et al. Meals and dephytinization affect calcium and zinc absorption in Nigerian children with rickets. Journal of Nutrition. 2009 May;139(5):926-32. PMID: 19321589.

30. Thacher TD, Fischer PR, Obadofin MO, et al. Comparison of metabolism of vitamins D2 and D3 in children with nutritional rickets. Journal of Bone & Mineral Research. 2010 Sep;25(9):1988-95. PMID: 20499377.

31. Thomas SDC, Need AG, Nordin BEC. Suppression of C-terminal telopeptide in hypovitaminosis D requires calcium as well as vitamin D. Calcified Tissue International. 2010 May;86(5):367-74. PMID: 20349229.

32. Wicherts IS, Boeke AJP, van der Meer IM, et al. Sunlight exposure or vitamin D supplementation for vitamin D-deficient non-western immigrants: a randomized clinical trial. Osteoporosis International. 2011 Mar;22(3):873-82. PMID: 20683712.

33. Valimaki MJ, Pekkarinen T, Velimaki VV, et al. The same annual dose of 292000 IU of vitamin D3 (cholecalciferol) on either daily or four monthly basis for elderly women: 1-year comparative study of the effects on serum 25(OH)D3 concentrations and renal function. Clinical Endocrinology; 2010. p. 455-61.

34. Eckardstein HAB-FBD-HESESWCWJOEHBSSWAJJSJHAV, Egli A. Oral supplementation with 25(OH)D3 versus vitamin D3: Effects on 25(OH)D levels, lower extremity function, blood pressure, and markers of innate immunity. Journal of Bone and Mineral Research; 2012. p. 160-9.

35. Golombick T, Diamond T. The effect of a combined oral calcium and vitamin D supplement for treating mild to moderate vitamin D deficiency in postmenopausal women. Clinical Interventions In Aging. 2008;3(1):183-6. PMID: 18488888.

36. Cipriani C, Romagnoli E, Pepe J, et al. Long-term bioavailability after a single oral or intramuscular administration of 600,000 IU of ergocalciferol or cholecalciferol: implications for treatment and prophylaxis. Journal of Clinical Endocrinology & Metabolism. 2013 Jul;98(7):2709-15. PMID: 23766519.

No Outcomes of Interest—N=306

1. Abnet CC, Chen Y, Chow W-H, et al. Circulating 25-hydroxyvitamin D and risk of esophageal and gastric cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. American Journal of Epidemiology. 2010 Jul 1;172(1):94-106. PMID: 20562192.

2. Abrams SA, Hawthorne KM, Chen Z. Supplementation with 1000 IU vitamin D/d leads to parathyroid hormone suppression, but not increased fractional calcium absorption, in 4-8-y-old children: a double-blind randomized controlled trial. American Journal of Clinical Nutrition. 2013 Jan;97(1):217-23. PMID: 23151536.

3. Afzal S, Bojesen SE, Nordestgaard BG. Low 25-hydroxyvitamin D and risk of type 2 diabetes: a prospective cohort study and metaanalysis. Clinical Chemistry. 2013 Feb;59(2):381-91. PMID: 23232064.

4. Afzal S, Nordestgaard BG, Bojesen SE. Plasma 25-hydroxyvitamin D and risk of non-melanoma and melanoma skin cancer: a prospective cohort study. Journal of Investigative Dermatology. 2013 Mar;133(3):629-36. PMID: 23190899.

5. Agarwal N, Faridi MMA, Aggarwal A, et al. Vitamin D Status of term exclusively breastfed infants and their mothers from India. Acta Paediatrica. 2010 Nov;99(11):1671-4. PMID: 20545930.

6. Agarwal N, Mithal A, Dhingra V, et al. Effect of two different doses of oral cholecalciferol supplementation on serum 25-hydroxy-vitamin D levels in healthy Indian postmenopausal women: A randomized controlled trial. Indian Journal of Endocrinology and Metabolism. 2013 Sep;17(5):883-9. PMID: 24083171.

7. Ahearn TU, McCullough ML, Flanders WD, et al. A randomized clinical trial of the effects of supplemental calcium and vitamin D3 on markers of their metabolism in normal mucosa of colorectal adenoma patients. Cancer Research. 2011 Jan 15;71(2):413-23. PMID: 21084270.

8. Ahearn TU, Shaukat A, Flanders WD, et al. A randomized clinical trial of the effects of supplemental calcium and vitamin D3 on the APC/-catenin pathway in the normal mucosa of colorectal adenoma patients. Cancer Prevention Research. 2012 Oct;5(10):1247-56. PMID: 22964475.

9. Al-Daghri NM, Alkharfy KM, Al-Saleh Y, et al. Modest reversal of metabolic syndrome manifestations with vitamin D status correction: a 12-month prospective study. Metabolism: Clinical & Experimental. 2012 May;61(5):661-6. PMID: 22075268.

10. Aloia J, Bojadzievski T, Yusupov E, et al. The relative influence of calcium intake and vitamin D status on serum parathyroid hormone and bone turnover biomarkers in a double-blind, placebo-controlled parallel group, longitudinal factorial design. Journal of Clinical Endocrinology & Metabolism. 2010 Jul;95(7):3216-24. PMID: 20463100.

11. Aloia JF, Dhaliwal R, Shieh A, et al. Calcium and vitamin d supplementation in postmenopausal women. Journal of Clinical Endocrinology & Metabolism. 2013 Nov;98(11):E1702-9. PMID: 24064695.

12. Aloia JF, Patel M, Dimaano R, et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. American Journal of Clinical Nutrition. 2008 Jun;87(6):1952-8. PMID: 18541590.

13. Alonso A, Rodriguez J, Carvajal I, et al. Prophylactic vitamin D in healthy infants: assessing the need. Metabolism: Clinical & Experimental. 2011 Dec;60(12):1719-25. PMID: 21663925.

14. Aluisio AR, Maroof Z, Chandramohan D, et al. Vitamin D3supplementation and childhood diarrhea: a randomized controlled trial. Pediatrics. 2013 Oct;132(4):e832-40. PMID: 24019420.

15. Amirbaigloo A, Hosseinpanah F, Sarvghadi F, et al. Absence of association between vitamin d deficiency and incident metabolic syndrome: tehran lipid and glucose study. Metabolic Syndrome & Related Disorders. 2013 Aug;11(4):236-42. PMID: 23496029.

16. Andersen R, Brot C, Mejborn H, et al. Vitamin D supplementation does not affect serum lipids and lipoproteins in Pakistani immigrants. European Journal of Clinical Nutrition. 2009 Sep;63(9):1150-3. PMID: 19352377.

17. Anderson JL, Vanwoerkom RC, Horne BD, et al. Parathyroid hormone, vitamin D, renal dysfunction, and cardiovascular disease: dependent or independent risk factors? American Heart Journal. 2011 Aug;162(2):331-9.e2. PMID: 21835295.

18. Annweiler C, Rolland Y, Schott AM, et al. Serum vitamin D deficiency as a predictor of incident non-Alzheimer dementias: a 7-year longitudinal study. Dementia & Geriatric Cognitive Disorders. 2011;32(4):273-8. PMID: 22261995.

19. Arabi A, Baddoura R, El-Rassi R, et al. PTH level but not 25 (OH) vitamin D level predicts bone loss rates in the elderly. Osteoporosis International. 2012 Mar;23(3):971-80. PMID: 21656018.

20. Arabi A, Zahed L, Mahfoud Z, et al. Vitamin D receptor gene polymorphisms modulate the skeletal response to vitamin D supplementation in healthy girls. Bone; 2009. p. 1091-7.

21. Arem H, Weinstein SJ, Horst RL, et al. Serum 25-hydroxyvitamin D and risk of oropharynx and larynx cancers in Finnish men. Cancer Epidemiology, Biomarkers & Prevention. 2011 Jun;20(6):1178-84. PMID: 21527582.

22. Arslan AA, Clendenen TV, Koenig KL, et al. Circulating vitamin d and risk of epithelial ovarian cancer. Journal of Oncology Print. 2009;2009:672492. PMID: 19727412.

23. Arvold DS, Odean MJ, Dornfeld MP, et al. Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial. Endocrine Practice. 2009 Apr;15(3):203-12. PMID: 19364687.

24. Arvold DS, Odean MJ, Dornfeld MP, et al. Correlation of symptoms with vitamin D deficiency and symptom response to cholecalciferol treatment: a randomized controlled trial. Endocrine Practice; 2009. p. 203-12.

25. Asemi Z, Samimi M, Tabassi Z, et al. Vitamin D supplementation affects serum high-sensitivity C-reactive protein, insulin resistance, and biomarkers of oxidative stress in pregnant women. Journal of Nutrition. 2013 Sep;143(9):1432-8. PMID: 23884390.

26. Asgari MM, Tang J, Warton ME, et al. Association of prediagnostic serum vitamin D levels with the development of basal cell carcinoma. Journal of Investigative Dermatology. 2010 May;130(5):1438-43. PMID: 20043012.

27. Atas E, Karademir F, Ersen A, et al. Comparison between daily supplementation doses of 200 versus 400 IU of vitamin D in infants. European Journal of Pediatrics. 2013 Aug;172(8):1039-42. PMID: 23559332.

28. Avenell A, Cook JA, MacLennan GS, et al. Vitamin D supplementation and type 2 diabetes: a substudy of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). Age & Ageing. 2009 Sep;38(5):606-9. PMID: 19617604.

29. Baker AM, Haeri S, Camargo CA, Jr., et al. First-trimester maternal vitamin D status and risk for gestational diabetes (GDM) a nested case-control study. Diabetes/Metabolism Research Reviews. 2012 Feb;28(2):164-8. PMID: 21818838.

30. Beilfuss J, Berg V, Sneve M, et al. Effects of a 1-year supplementation with cholecalciferol on interleukin-6, tumor necrosis factor-alpha and insulin resistance in overweight and obese subjects. Cytokine. 2012 Dec;60(3):870-4. PMID: 22925537.

31. Belenchia AM, Tosh AK, Hillman LS, et al. Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. American Journal of Clinical Nutrition. 2013 Apr;97(4):774-81. PMID: 23407306.

32. Benjamin A, Moriakova A, Akhter N, et al. Determinants of 25-hydroxyvitamin D levels in African-American and Caucasian male veterans. Osteoporosis International. 2009 Oct;20(10):1795-803. PMID: 19280273.

33. Bergink AP, Uitterlinden AG, Van Leeuwen JPTM, et al. Vitamin D status, bone mineral density, and the development of radiographic osteoarthritis of the knee: The Rotterdam Study. JCR: Journal of Clinical Rheumatology. 2009 Aug;15(5):230-7. PMID: 19654490.

34. Bertone-Johnson ER, Powers SI, Spangler L, et al. Vitamin D supplementation and depression in the women's health initiative calcium and vitamin D trial. American Journal of Epidemiology. 2012 Jul 1;176(1):1-13. PMID: 22573431.

35. Biancuzzo RM, Clarke N, Reitz RE, et al. Serum concentrations of 1,25-dihydroxyvitamin d2 and 1,25-dihydroxyvitamin d3 in response to vitamin d2 and vitamin d3 supplementation. Journal of Clinical Endocrinology & Metabolism. 2013 Mar;98(3):973-9. PMID: 23386645.

36. Biancuzzo RM, Young A, Bibuld D, et al. Fortification of orange juice with vitamin D(2) or vitamin D(3) is as effective as an oral supplement in maintaining vitamin D status in adults. American Journal of Clinical Nutrition. 2010 Jun;91(6):1621-6. PMID: 20427729.

37. Binkley N, Gemar D, Engelke J, et al. Evaluation of ergocalciferol or cholecalciferol dosing, 1,600 IU daily or 50,000 IU monthly in older adults. Journal of Clinical Endocrinology & Metabolism. 2011 Apr;96(4):981-8. PMID: 21289249.

38. Binkley N, Ringe JD, Reed JI, et al. Alendronate/vitamin D3 70 mg/2800 IU with and without additional 2800 IU vitamin D3 for osteoporosis: results from the 24-week extension of a 15-week randomized, controlled trial. Bone. 2009 Apr;44(4):639-47. PMID: 19185560.

39. Bischoff-Ferrari HA, Dawson-Hughes B, Platz A, et al. Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: a randomized controlled trial. Archives of Internal Medicine. 2010 May 10;170(9):813-20. PMID: 20458090.

40. Boer IH, Tinker LF, Connelly S, et al. Calcium plus vitamin D supplementation and the risk of incident diabetes in the women's health initiative. Diabetes Care; 2008. p. 701-7TN: NCT00000611/ClinicalTrials.gov.

41. Bonjour J-P, Benoit V, Rousseau B, et al. Consumption of vitamin D-and calcium-fortified soft white cheese lowers the biochemical marker of bone resorption TRAP 5b in postmenopausal women at moderate risk of osteoporosis fracture. Journal of Nutrition. 2012 Apr;142(4):698-703. PMID: 22357739.

42. Breen ME, Laing EM, Hall DB, et al. 25-hydroxyvitamin D, insulin-like growth factor-I, and bone mineral accrual during growth. Journal of Clinical Endocrinology & Metabolism. 2011 Jan;96(1):E89-98. PMID: 20962027.

43. Breitling LP, Perna L, Muller H, et al. Vitamin D and cognitive functioning in the elderly population in Germany. Experimental Gerontology. 2012 Jan;47(1):122-7. PMID: 22123431.

44. Brunel E, Schnitzler M, Foidart-Dessalle M, et al. A Double-Blind, Placebo Controlled, Randomized Trial to Assess the Impact of a Monthly Administration of 50,000 IU of Vitamin D3 for 6 Months on Serum Levels of 25-Hydroxyvitamin D in Healthy Young Adults. International Journal of Endocrinology Print. 2013;2013:652648. PMID: 24324493.

45. Burnett-Bowie S-AM, Leder BZ, Henao MP, et al. Randomized trial assessing the effects of ergocalciferol administration on circulating FGF23. Clinical Journal of The American Society of Nephrology: CJASN. 2012 Apr;7(4):624-31. PMID: 22300739.

46. Candido FG, Silva Ton WT, Goncalves Alfenas Rde C. Dairy products consumption versus type 2 diabetes prevention and treatment; a review of recent findings from human studies. Nutricion Hospitalaria. 2013 Sep-Oct;28(5):1384-95. PMID: 24160191.

47. Carnes J, Quinn S, Nelson M, et al. Intermittent high-dose vitamin D corrects vitamin D deficiency in adolescents: a pilot study. European Journal of Clinical Nutrition. 2012 Apr;66(4):530-2. PMID: 22190133.

48. Carter GD, Jones JC. Use of a common standard improves the performance of liquid chromatography-tandem mass spectrometry methods for serum 25-hydroxyvitamin-D.[Erratum appears in Ann Clin Biochem. 2009 Sep;46(Pt 5):434]. Annals of Clinical Biochemistry. 2009 Jan;46(Pt 1):79-81. PMID: 19103962.

49. Cashman KD, FitzGerald AP, Viljakainen HT, et al. Estimation of the dietary requirement for vitamin D in healthy adolescent white girls. American Journal of Clinical Nutrition. 2011 Mar;93(3):549-55. PMID: 21270380.

50. Cashman KD, Hill TR, Lucey AJ, et al. Estimation of the dietary requirement for vitamin D in healthy adults. The American journal of clinical nutrition; 2008. p. 1535-42.

51. Cashman KD, Seamans KM, Lucey AJ, et al. Relative effectiveness of oral 25-hydroxyvitamin D3 and vitamin D3 in raising wintertime serum 25-hydroxyvitamin D in older adults. American Journal of Clinical Nutrition. 2012 Jun;95(6):1350-6. PMID: 22552038.

52. Cashman KD, Wallace JM, Horigan G, et al. Estimation of the dietary requirement for vitamin D in free-living adults >=64 y of age. American Journal of Clinical Nutrition. 2009 May;89(5):1366-74. PMID: 19297462.

53. Cavalier E, Fache W, Souberbielle J-C. A Randomised, Double-Blinded, Placebo-Controlled, Parallel Study of Vitamin D3 Supplementation with Different Schemes Based on Multiples of 25,000IU Doses. International Journal of Endocrinology Print. 2013;2013:327265. PMID: 23431293.

54. Cavalli L, Cavalli T, Marcucci G, et al. Biological effects of various regimes of 25-hydroxyvitamin D3 (calcidiol) administration on bone mineral metabolism in postmenopausal women. Clinical Cases in Mineral & Bone Metabolism. 2009 May;6(2):169-73. PMID: 22461169.

55. Cherniack EP, Florez HJ, Hollis BW, et al. The response of elderly veterans to daily vitamin D3 supplementation of 2,000 IU: a pilot efficacy study. Journal of the American Geriatrics Society. 2011 Feb;59(2):286-90. PMID: 21288233.

56. Chung H-Y, Chin SO, Kang M-IL, et al. Efficacy of risedronate with cholecalciferol on 25-hydroxyvitamin D level and bone turnover in Korean patients with osteoporosis. Clinical Endocrinology. 2011 Jun;74(6):699-704. PMID: 21521310.

57. Close GL, Russell J, Cobley JN, et al. Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: implications for skeletal muscle function. Journal of Sports Sciences. 2013;31(4):344-53. PMID: 23083379.

58. Cremers E, Thijs C, Penders J, et al. Maternal and child's vitamin D supplement use and vitamin D level in relation to childhood lung function: the KOALA Birth Cohort Study. Thorax. 2011 Jun;66(6):474-80. PMID: 21422038.

59. Crozier SR, Harvey NC, Inskip HM, et al. Maternal vitamin D status in pregnancy is associated with adiposity in the offspring: findings from the Southampton Women's Survey. American Journal of Clinical Nutrition. 2012 Jul;96(1):57-63. PMID: 22623747.

60. Curtis JR, Ewing SK, Bauer DC, et al. Association of intact parathyroid hormone levels with subsequent hip BMD loss: the Osteoporotic Fractures in Men (MrOS) Study. Journal of Clinical Endocrinology & Metabolism. 2012 Jun;97(6):1937-44. PMID: 22442276.

61. Daly RM, Petrass N, Bass S, et al. The skeletal benefits of calcium- and vitamin D3-fortified milk are sustained in older men after withdrawal of supplementation: an 18-mo follow-up study. American Journal of Clinical Nutrition; 2008. p. 771-7.

62. Darling AL, Hart KH, Macdonald HM, et al. Vitamin D deficiency in UK South Asian Women of childbearing age: a comparative longitudinal investigation with UK Caucasian women. Osteoporosis International. 2013 Feb;24(2):477-88. PMID: 22525977.

63. Dean AJ, Bellgrove MA, Hall T, et al. Effects of vitamin D supplementation on cognitive and emotional functioning in young adults--a randomised controlled trial. PLoS ONE [Electronic Resource]. 2011;6(11):e25966. PMID: 22073146.

64. Deleskog A, Hilding A, Brismar K, et al. Low serum 25-hydroxyvitamin D level predicts progression to type 2 diabetes in individuals with prediabetes but not with normal glucose tolerance. Diabetologia. 2012 Jun;55(6):1668-78. PMID: 22426800.

65. Deng X, Song Y, Manson JE, et al. Magnesium, vitamin D status and mortality: results from US National Health and Nutrition Examination Survey (NHANES) 2001 to 2006 and NHANES III. BMC Medicine. 2013;11:187. PMID: 23981518.

66. Dennis NA, Houghton LA, Jones GT, et al. The level of serum anti-Mullerian hormone correlates with vitamin D status in men and women but not in boys. Journal of Clinical Endocrinology & Metabolism. 2012 Jul;97(7):2450-5. PMID: 22508713.

67. Diamond T, Wong YK, Golombick T. Effect of oral cholecalciferol 2,000 versus 5,000 IU on serum vitamin D, PTH, bone and muscle strength in patients with vitamin D deficiency. Osteoporosis International. 2013 Mar;24(3):1101-5. PMID: 22422304.

68. Ding C, Parameswaran V, Blizzard L, et al. Not a simple fat-soluble vitamin: Changes in serum 25-(OH)D levels are predicted by adiposity and adipocytokines in older adults. Journal of Internal Medicine. 2010 Nov;268(5):501-10. PMID: 20804516.

69. Dong Y, Stallmann-Jorgensen IS, Pollock NK, et al. A 16-week randomized clinical trial of 2000 international units daily vitamin D3 supplementation in black youth: 25-hydroxyvitamin D, adiposity, and arterial stiffness. Journal of Clinical Endocrinology & Metabolism. 2010 Oct;95(10):4584-91. PMID: 20660028.

70. Dror Y, Giveon SM, Hoshen M, et al. Vitamin D levels for preventing acute coronary syndrome and mortality: evidence of a nonlinear association. Journal of Clinical Endocrinology & Metabolism. 2013 May;98(5):2160-7. PMID: 23533239.

71. Eide MJ, Johnson DA, Jacobsen GR, et al. Vitamin D and nonmelanoma skin cancer in a health maintenance organization cohort. Archives of Dermatology. 2011 Dec;147(12):1379-84. PMID: 21844426.

72. Emel T, Dogan DA, Erdem G, et al. Therapy strategies in vitamin D deficiency with or without rickets: efficiency of low-dose stoss therapy. Journal of Pediatric Endocrinology. 2012;25(1-2):107-10. PMID: 22570958.

73. Ensrud KE, Blackwell TL, Cauley JA, et al. Circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study. Journal of the American Geriatrics Society. 2011 Jan;59(1):101-6. PMID: 21226680.

74. Ensrud KE, Ewing SK, Fredman L, et al. Circulating 25-hydroxyvitamin D levels and frailty status in older women. Journal of Clinical Endocrinology & Metabolism. 2010 Dec;95(12):5266-73. PMID: 21131545.

75. Ensrud KE, Taylor BC, Paudel ML, et al. Serum 25-hydroxyvitamin D levels and rate of hip bone loss in older men. Journal of Clinical Endocrinology & Metabolism. 2009 Aug;94(8):2773-80. PMID: 19454586.

76. Farid K, Volpe-Gillot L, Petras S, et al. Correlation between serum 25-hydroxyvitamin D concentrations and regional cerebral blood flow in degenerative dementia. Nuclear Medicine Communications. 2012 Oct;33(10):1048-52. PMID: 22773150.

77. Fedirko V, Bostick RM, Flanders WD, et al. Effects of vitamin D and calcium supplementation on markers of apoptosis in normal colon mucosa: a randomized, double-blind, placebo-controlled clinical trial. Cancer Prevention Research. 2009 Mar;2(3):213-23. PMID: 19258546.

78. Fedirko V, Bostick RM, Flanders WD, et al. Effects of vitamin d and calcium on proliferation and differentiation in normal colon mucosa: a randomized clinical trial. Cancer Epidemiology, Biomarkers & Prevention. 2009 Nov;18(11):2933-41. PMID: 19861511.

79. Forouhi NG, Luan Ja, Cooper A, et al. Baseline serum 25-hydroxy vitamin d is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990-2000. Diabetes. 2008 Oct;57(10):2619-25. PMID: 18591391.

80. Forsythe LK, Livingstone MBE, Barnes MS, et al. Effect of adiposity on vitamin D status and the 25-hydroxycholecalciferol response to supplementation in healthy young and older Irish adults. British Journal of Nutrition. 2012 Jan;107(1):126-34. PMID: 21733320.

81. Gagnon C, Lu ZX, Magliano DJ, et al. Low serum 25-hydroxyvitamin D is associated with increased risk of the development of the metabolic syndrome at five years: results from a national, population-based prospective study (The Australian Diabetes, Obesity and Lifestyle Study: AusDiab). Journal of Clinical Endocrinology & Metabolism. 2012 Jun;97(6):1953-61. PMID: 22442263.

82. Gagnon C, Lu ZX, Magliano DJ, et al. Serum 25-hydroxyvitamin D, calcium intake, and risk of type 2 diabetes after 5 years: results from a national, population-based prospective study (the Australian Diabetes, Obesity and Lifestyle study). Diabetes Care. 2011 May;34(5):1133-8. PMID: 21430082.

83. Gallagher JC, Jindal PS, Smith LM. Vitamin d supplementation in young white and african american women. Journal of Bone & Mineral Research. 2014 Jan;29(1):173-81. PMID: 23761326.

84. Gallagher JC, Peacock M, Yalamanchili V, et al. Effects of vitamin d supplementation in older african american women. Journal of Clinical Endocrinology & Metabolism. 2013 Mar;98(3):1137-46. PMID: 23386641.

85. Gallagher JC, Sai A, Templin T, et al. Dose response to vitamin D supplementation in postmenopausal women: a randomized trial. Annals of internal medicine; 2012. p. 425-37.

86. Gallagher JC, Yalamanchili V, Smith LM. The effect of vitamin D on calcium absorption in older women. Journal of Clinical Endocrinology & Metabolism. 2012 Oct;97(10):3550-6. PMID: 22855333.

87. Gallicchio L, Moore LE, Stevens VL, et al. Circulating 25-hydroxyvitamin D and risk of kidney cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. American Journal of Epidemiology. 2010 Jul 1;172(1):47-57. PMID: 20562187.

88. Genazzani AR, Stomati M, Valentino V, et al. Effect of 1-year, low-dose DHEA therapy on climacteric symptoms and female sexuality. Climacteric. 2011 Dec;14(6):661-8. PMID: 21942655.

89. Gernand AD, Bodnar LM, Klebanoff MA, et al. Maternal serum 25-hydroxyvitamin D and placental vascular pathology in a multicenter US cohort. American Journal of Clinical Nutrition. 2013 Aug;98(2):383-8. PMID: 23803889.

90. Ghazi AA, Hosseinpanah F, M Ardakani E, et al. Effects of different doses of oral cholecalciferol on serum 25(OH)D, PTH, calcium and bone markers during fall and winter in schoolchildren. European Journal of Clinical Nutrition. 2010 Dec;64(12):1415-22. PMID: 20823895.

91. Giapros VI, Schiza V, Challa AS, et al. Vitamin D and parathormone levels of late-preterm formula fed infants during the first year of life. European Journal of Clinical Nutrition. 2012 Feb;66(2):224-30. PMID: 21897423.

92. Glendenning P, Zhu K, Inderjeeth C, et al. Effects of three-monthly oral 150,000 IU cholecalciferol supplementation on falls, mobility, and muscle strength in older postmenopausal women: a randomized controlled trial. Journal of Bone & Mineral Research. 2012 Jan;27(1):170-6. PMID: 21956713.

93. Gonzalez-Molero I, Rojo-Martinez G, Morcillo S, et al. Vitamin D and incidence of diabetes: a prospective cohort study. Clinical Nutrition. 2012 Aug;31(4):571-3. PMID: 22204964.

94. Gorai I, Hattori S, Tanaka Y, et al. Alfacalcidol-supplemented raloxifene therapy has greater bone-sparing effect than raloxifene-alone therapy in postmenopausal Japanese women with osteoporosis or osteopenia. Journal of Bone & Mineral Metabolism. 2012 May;30(3):349-58. PMID: 22130786.

95. Gordon CM, Williams AL, Feldman HA, et al. Treatment of hypovitaminosis D in infants and toddlers. Journal of Clinical Endocrinology & Metabolism. 2008 Jul;93(7):2716-21. PMID: 18413426.

96. Gorham ED, Garland CF, Burgi AA, et al. Lower prediagnostic serum 25-hydroxyvitamin D concentration is associated with higher risk of insulin-requiring diabetes: a nested case-control study. Diabetologia. 2012 Dec;55(12):3224-7. PMID: 22955995.

97. Goswami R, Gupta N, Ray D, et al. Pattern of 25-hydroxy vitamin D response at short (2 month) and long (1 year) interval after 8 weeks of oral supplementation with cholecalciferol in Asian Indians with chronic hypovitaminosis D. British Journal of Nutrition. 2008 Sep;100(3):526-9. PMID: 18252022.

98. Goswami R, Vatsa M, Sreenivas V, et al. Skeletal muscle strength in young Asian Indian females after vitamin D and calcium supplementation: a double-blind randomized controlled clinical trial. Journal of Clinical Endocrinology & Metabolism. 2012 Dec;97(12):4709-16. PMID: 22904178.

99. Green TJ, Skeaff CM, Rockell JE. Milk fortified with the current adequate intake for vitamin D (5 microg) increases serum 25-hydroxyvitamin D compared to control milk but is not sufficient to prevent a seasonal decline in young women. Asia Pacific journal of clinical nutrition; 2010. p. 195-9.

100. Greene DA, Naughton GA. Calcium and vitamin-D supplementation on bone structural properties in peripubertal female identical twins: a randomised controlled trial. Osteoporosis International. 2011 Feb;22(2):489-98. PMID: 20544178.

101. Griffin FC, Gadegbeku CA, Sowers MR. Vitamin D and subsequent systolic hypertension among women. American Journal of Hypertension. 2011 Mar;24(3):316-21. PMID: 21088670.

102. Grimnes G, Figenschau Y, Almas B, et al. Vitamin D, insulin secretion, sensitivity, and lipids: results from a case-control study and a randomized controlled trial using hyperglycemic clamp technique. Diabetes. 2011 Nov;60(11):2748-57. PMID: 21911741.

103. Gupta R, Sharma U, Gupta N, et al. Effect of cholecalciferol and calcium supplementation on muscle strength and energy metabolism in vitamin D-deficient Asian Indians: a randomized, controlled trial. Clinical Endocrinology. 2010 Oct;73(4):445-51. PMID: 20455886.

104. Haliloglu B, Ilter E, Aksungar FB, et al. Bone turnover and maternal 25(OH) vitamin D3 levels during pregnancy and the postpartum period: should routine vitamin D supplementation be increased in pregnant women? European Journal of Obstetrics, Gynecology, & Reproductive Biology. 2011 Sep;158(1):24-7. PMID: 21543150.

105. Harris RA, Pedersen-White J, Guo D-H, et al. Vitamin D3 supplementation for 16 weeks improves flow-mediated dilation in overweight African-American adults. American Journal of Hypertension. 2011 May;24(5):557-62. PMID: 21311504.

106. Heine G, Drozdenko G, Lahl A, et al. Efficient tetanus toxoid immunization on vitamin D supplementation. European Journal of Clinical Nutrition. 2011 Mar;65(3):329-34. PMID: 21224870.

107. Hettiarachchi M, Liyanage C. Efficacy of ‘Thriposha’ supplementation in improving the micronutrient status of preschool children. Ceylon Medical Journal. 2010 Sep;55(3):85-9. PMID: 21033304.

108. Hirschler V, Maccallini G, Sanchez MS, et al. Improvement in high-density lipoprotein cholesterol levels in argentine Indian school children after vitamin d supplementation. Hormone research in pdiatrics. 2013;80(5):335-42. PMID: 24217313.

109. Holecki M, Zahorska-Markiewicz B, Chudek J, et al. Changes in bone mineral density and bone turnover markers in obese women after short-term weight loss therapy during a 5-year follow-up. Polskie Archiwum Medycyny Wewnetrznej. 2010 Jul;120(7-8):248-54. PMID: 20693954.

110. Holick MF, Biancuzzo RM, Chen TC, et al. Vitamin D2 is as effective as vitamin D3 in maintaining circulating concentrations of 25-hydroxyvitamin D. Journal of Clinical Endocrinology & Metabolism. 2008 Mar;93(3):677-81. PMID: 18089691.

111. Holick MF, Lamb JJ, Lerman RH, et al. Hop rho iso-alpha acids, berberine, vitamin D3 and vitamin K1 favorably impact biomarkers of bone turnover in postmenopausal women in a 14-week trial. Journal of Bone & Mineral Metabolism. 2010 May;28(3):342-50. PMID: 20024591.

112. Hoogendijk WJG, Lips P, Dik MG, et al. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Archives of General Psychiatry. 2008 May;65(5):508-12. PMID: 18458202.

113. Houghton LA, Gray AR, Szymlek-Gay EA, et al. Vitamin D-fortified milk achieves the targeted serum 25-hydroxyvitamin D concentration without affecting that of parathyroid hormone in New Zealand toddlers. The Journal of nutrition; 2011. p. 1840-6.

114. Ilahi M, Armas LA, Heaney RP. Pharmacokinetics of a single, large dose of cholecalciferol. The American journal of clinical nutrition; 2008. p. 688-91.

115. Ioannou C, Javaid MK, Mahon P, et al. The effect of maternal vitamin D concentration on fetal bone. Journal of Clinical Endocrinology & Metabolism. 2012 Nov;97(11):E2070-7. PMID: 22990090.

116. Jorde R, Figenschau Y, Emaus N, et al. Serum 25-hydroxyvitamin D levels are strongly related to systolic blood pressure but do not predict future hypertension. Hypertension. 2010 Mar;55(3):792-8. PMID: 20065152.

117. Jorde R, Sneve M, Emaus N, et al. Cross-sectional and longitudinal relation between serum 25-hydroxyvitamin D and body mass index: the Tromso study. European Journal of Nutrition. 2010 Oct;49(7):401-7. PMID: 20204652.

118. Jorde R, Sneve M, Figenschau Y, et al. Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. Journal of Internal Medicine. 2008 Dec;264(6):599-609. PMID: 18793245.

119. Jorde R, Sneve M, Hutchinson M, et al. Tracking of serum 25-hydroxyvitamin D levels during 14 years in a population-based study and during 12 months in an intervention study. American Journal of Epidemiology. 2010 Apr 15;171(8):903-8. PMID: 20219763.

120. Jorde R, Sneve M, Torjesen P, et al. Parameters of the thrombogram are associated with serum 25-hydroxyvitamin D levels at baseline, but not affected during supplementation with vitamin D. Thrombosis Research. 2010 May;125(5):e210-3. PMID: 20071011.

121. Jorde R, Sneve M, Torjesen PA, et al. No effect of supplementation with cholecalciferol on cytokines and markers of inflammation in overweight and obese subjects. Cytokine. 2010 May;50(2):175-80. PMID: 20122848.

122. Jorde R, Strand Hutchinson M, Kjaergaard M, et al. Supplementation with High Doses of Vitamin D to Subjects without Vitamin D Deficiency May Have Negative Effects: Pooled Data from Four Intervention Trials in Tromso. Isrn Endocrinology Print. 2013;2013:348705. PMID: 23577264.

123. Kaats GR, Preuss HG, Croft HA, et al. A comparative effectiveness study of bone density changes in women over 40 following three bone health plans containing variations of the same novel plant-sourced calcium. International Journal of Medical Sciences. 2011;8(3):180-91. PMID: 21448303.

124. Kabadi SM, Liu L, Auchincloss AH, et al. Multivariate path analysis of serum 25-hydroxyvitamin D concentration, inflammation, and risk of type 2 diabetes mellitus. Disease Markers. 2013;35(3):187-93. PMID: 24167365.

125. Kamycheva E, Berg V, Jorde R. Insulin-like growth factor I, growth hormone, and insulin sensitivity: the effects of a one-year cholecalciferol supplementation in middle-aged overweight and obese subjects. Endocrine. 2013 Apr;43(2):412-8. PMID: 23109222.

126. Kayaniyil S, Retnakaran R, Harris SB, et al. Prospective associations of vitamin D with -cell function and glycemia: the PROspective Metabolism and ISlet cell Evaluation (PROMISE) cohort study. Diabetes. 2011 Nov;60(11):2947-53. PMID: 21911752.

127. Khajehei M, Abdali K, Parsanezhad ME, et al. Effect of treatment with dydrogesterone or calcium plus vitamin D on the severity of premenstrual syndrome. International Journal of Gynaecology & Obstetrics. 2009 May;105(2):158-61. PMID: 19232611.

128. Khajehei M, Abdali K, Tabatabaee HR. A comparison between the efficacy of dydrogesterone and calcium plus vitamin D in improving women's general health. African Journal of Psychiatry. 2010 Jul;13(3):218-24. PMID: 20957321.

129. Khoraminya N, Tehrani-Doost M, Jazayeri S, et al. Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. Australian & New Zealand Journal of Psychiatry. 2013 Mar;47(3):271-5. PMID: 23093054.

130. Kilkkinen A, Knekt P, Heliovaara M, et al. Vitamin D status and the risk of lung cancer: a cohort study in Finland. Cancer Epidemiology, Biomarkers & Prevention. 2008 Nov;17(11):3274-8. PMID: 18990771.

131. Kislal FM, Dilmen U. Effect of different doses of vitamin D on osteocalcin and deoxypyridinoline in preterm infants. Pediatrics International. 2008 Apr;50(2):204-7. PMID: 18353060.

132. Kjaergaard M, Waterloo K, Wang CEA, et al. Effect of vitamin D supplement on depression scores in people with low levels of serum 25-hydroxyvitamin D: nested case-control study and randomised clinical trial. British Journal of Psychiatry. 2012 Nov;201(5):360-8. PMID: 22790678.

133. Knekt P, Laaksonen M, Mattila C, et al. Serum vitamin D and subsequent occurrence of type 2 diabetes. Epidemiology. 2008 Sep;19(5):666-71. PMID: 18496468.

134. Knight JA, Wong J, Blackmore KM, et al. Vitamin D association with estradiol and progesterone in young women. Cancer Causes & Control. 2010 Mar;21(3):479-83. PMID: 19916051.

135. Kull M, Jr., Kallikorm R, Tamm A, et al. Seasonal variance of 25-(OH) vitamin D in the general population of Estonia, a Northern European country. BMC Public Health. 2009;9:22. PMID: 19152676.

136. Kumar GT, Sachdev HS, Chellani H, et al. Effect of weekly vitamin D supplements on mortality, morbidity, and growth of low birthweight term infants in India up to age 6 months: randomised controlled trial. BMJ. 2011;342:d2975. PMID: 21628364.

137. Lagari VS, Gomez-Marin O, Levis S. Differences in vitamin D3 dosing regimens in a geriatric community-dwelling population. Endocrine Practice. 2012 Nov-Dec;18(6):847-54. PMID: 22784845.

138. Lalla RV, Choquette LE, Feinn RS, et al. Multivitamin therapy for recurrent aphthous stomatitis: a randomized, double-masked, placebo-controlled trial. Journal of the American Dental Association. 2012 Apr;143(4):370-6. PMID: 22467697.

139. Lalor MK, Floyd S, Gorak-Stolinska P, et al. BCG vaccination: a role for vitamin D? PLoS ONE [Electronic Resource]. 2011;6(1):e16709. PMID: 21304967.

140. Lamb JJ, Holick MF, Lerman RH, et al. Nutritional supplementation of hop rho iso-alpha acids, berberine, vitamin D3, and vitamin K1 produces a favorable bone biomarker profile supporting healthy bone metabolism in postmenopausal women with metabolic syndrome. Nutrition Research. 2011 May;31(5):347-55. PMID: 21636012.

141. Lasco A, Catalano A, Benvenga S. Improvement of primary dysmenorrhea caused by a single oral dose of vitamin D: Results of a randomized, double-blind, placebo-controlled study. Archives of internal medicine; 2012. p. 366-7.

142. Lawlor DA, Wills AK, Fraser A, et al. Association of maternal vitamin D status during pregnancy with bone-mineral content in offspring: a prospective cohort study. Lancet. 2013 Jun 22;381(9884):2176-83. PMID: 23518316.

143. LeBlanc ES, Rizzo JH, Pedula KL, et al. Associations between 25-hydroxyvitamin D and weight gain in elderly women. Journal of Women's Health. 2012 Oct;21(10):1066-73. PMID: 22731629.

144. Leidig-Bruckner G, Roth HJ, Bruckner T, et al. Are commonly recommended dosages for vitamin D supplementation too low? Vitamin D status and effects of supplementation on serum 25-hydroxyvitamin D levels--an observational study during clinical practice conditions. Osteoporosis International. 2011 Jan;22(1):231-40. PMID: 20556359.

145. Lewis RM, Redzic M, Thomas DT. The effects of season-long vitamin d supplementation on collegiate swimmers and divers. International Journal of Sport Nutrition & Exercise Metabolism. 2013 Oct;23(5):431-40. PMID: 23475128.

146. Liang G, Nan H, Qureshi AA, et al. Pre-diagnostic plasma 25-hydroxyvitamin D levels and risk of non-melanoma skin cancer in women. PLoS ONE [Electronic Resource]. 2012;7(4):e35211. PMID: 22493740.

147. Lim S, Kim MJ, Choi SH, et al. Association of vitamin D deficiency with incidence of type 2 diabetes in high-risk Asian subjects. American Journal of Clinical Nutrition. 2013 Mar;97(3):524-30. PMID: 23364011.

148. Lim U, Freedman DM, Hollis BW, et al. A prospective investigation of serum 25-hydroxyvitamin D and risk of lymphoid cancers. International Journal of Cancer. 2009 Feb 15;124(4):979-86. PMID: 19035445.

149. Llewellyn DJ, Lang IA, Langa KM, et al. Vitamin D and risk of cognitive decline in elderly persons. Archives of Internal Medicine. 2010 Jul 12;170(13):1135-41. PMID: 20625021.

150. Lutz LJ, Karl JP, Rood JC, et al. Vitamin D status, dietary intake, and bone turnover in female Soldiers during military training: a longitudinal study. Journal of the International Society of Sports Nutrition. 2012;9(1):38. PMID: 22866974.

151. Maalouf J, Nabulsi M, Vieth R, et al. Short- and long-term safety of weekly high-dose vitamin D3 supplementation in school children. Journal of Clinical Endocrinology & Metabolism. 2008 Jul;93(7):2693-701. PMID: 18445674.

152. Madar AA, Klepp KI, Meyer HE. Effect of free vitamin D(2) drops on serum 25-hydroxyvitamin D in infants with immigrant origin: a cluster randomized controlled trial. European Journal of Clinical Nutrition. 2009 Apr;63(4):478-84. PMID: 18231120.

153. Mahon P, Harvey N, Crozier S, et al. Low maternal vitamin D status and fetal bone development: cohort study. Journal of Bone & Mineral Research. 2010 Jan;25(1):14-9. PMID: 19580464.

154. Mai X-M, Chen Y, Camargo CA, Jr., et al. Cross-sectional and prospective cohort study of serum 25-hydroxyvitamin D level and obesity in adults: the HUNT study. American Journal of Epidemiology. 2012 May 15;175(10):1029-36. PMID: 22312120.

155. Major GC, Alarie FP, Dore J, et al. Calcium plus vitamin D supplementation and fat mass loss in female very low-calcium consumers: potential link with a calcium-specific appetite control. British Journal of Nutrition. 2009 Mar;101(5):659-63. PMID: 19263591.

156. Major JM, Graubard BI, Dodd KW, et al. Variability and reproducibility of circulating vitamin D in a nationwide U.S. population. Journal of Clinical Endocrinology & Metabolism. 2013 Jan;98(1):97-104. PMID: 23144464.

157. Major JM, Kiruthu C, Weinstein SJ, et al. Pre-diagnostic circulating vitamin D and risk of melanoma in men. PLoS ONE [Electronic Resource]. 2012;7(4):e35112. PMID: 22558121.

158. Malhotra N, Mithal A, Gupta S, et al. Effect of vitamin D supplementation on bone health parameters of healthy young Indian women. Archives of Osteoporosis; 2009. p. 47-53.

159. Manios Y, Moschonis G, Koutsikas K, et al. Changes in body composition following a dietary and lifestyle intervention trial: the postmenopausal health study. Maturitas. 2009 Jan 20;62(1):58-65. PMID: 19118956.

160. Manios Y, Moschonis G, Lyritis GP. Seasonal variations of vitamin D status in Greek postmenopausal women receiving enriched dairy products for 30 months: the Postmenopausal Health Study. European Journal of Clinical Nutrition. 2011 Mar;65(3):412-4. PMID: 21224868.

161. Manios Y, Moschonis G, Panagiotakos DB, et al. Changes in biochemical indices of bone metabolism in post-menopausal women following a dietary intervention with fortified dairy products. Journal of Human Nutrition & Dietetics. 2009 Apr;22(2):156-65. PMID: 19226352.

162. Manson JE, Allison MA, Carr JJ, et al. Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. Menopause. 2010 Jul;17(4):683-91. PMID: 20551849.

163. Margolis KL, Martin LW, Ray RM, et al. A prospective study of serum 25-hydroxyvitamin D levels, blood pressure, and incident hypertension in postmenopausal women. American Journal of Epidemiology. 2012 Jan 1;175(1):22-32. PMID: 22127681.

164. McAlindon T, LaValley M, Schneider E, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. JAMA. 2013 Jan 9;309(2):155-62. PMID: 23299607.

165. McCullough ML, Bandera EV, Moore DF, et al. Vitamin D and calcium intake in relation to risk of endometrial cancer: a systematic review of the literature. Preventive Medicine. 2008 Apr;46(4):298-302. PMID: 18155758.

166. McCullough ML, Bostick RM, Daniel CR, et al. Vitamin D status and impact of vitamin D3 and/or calcium supplementation in a randomized pilot study in the Southeastern United States. Journal of the American College of Nutrition. 2009 Dec;28(6):678-86. PMID: 20516268.

167. McGrath JJ, Eyles DW, Pedersen CB, et al. Neonatal vitamin D status and risk of schizophrenia: a population-based case-control study. Archives of General Psychiatry. 2010 Sep;67(9):889-94. PMID: 20819982.

168. Meng JE, Hovey KM, Wactawski-Wende J, et al. Intraindividual variation in plasma 25-hydroxyvitamin D measures 5 years apart among postmenopausal women. Cancer Epidemiology, Biomarkers & Prevention. 2012 Jun;21(6):916-24. PMID: 22523182.

169. Merewood A, Mehta SD, Grossman X, et al. Vitamin D status among 4-month-old infants in New England: a prospective cohort study. Journal of Human Lactation. 2012 May;28(2):159-66. PMID: 22526344.

170. Milaneschi Y, Shardell M, Corsi AM, et al. Serum 25-hydroxyvitamin D and depressive symptoms in older women and men. Journal of Clinical Endocrinology & Metabolism. 2010 Jul;95(7):3225-33. PMID: 20444911.

171. Millen AE, Wactawski-Wende J, Pettinger M, et al. Predictors of serum 25-hydroxyvitamin D concentrations among postmenopausal women: the Women's Health Initiative Calcium plus Vitamin D clinical trial. American Journal of Clinical Nutrition. 2010 May;91(5):1324-35. PMID: 20219959.

172. Miricescu D, Totan A, Calenic B, et al. Salivary biomarkers: Relationship between oxidative stress and alveolar bone loss in chronic periodontitis. Acta Odontologica Scandinavica. 2014 Jan;72(1):42-7. PMID: 23869629.

173. Mitri J, Dawson-Hughes B, Hu FB, et al. Effects of vitamin D and calcium supplementation on pancreatic cell function, insulin sensitivity, and glycemia in adults at high risk of diabetes: the Calcium and Vitamin D for Diabetes Mellitus (CaDDM) randomized controlled trial. American Journal of Clinical Nutrition. 2011 Aug;94(2):486-94. PMID: 21715514.

174. Mohamed WA, Al-Shehri MA. Cord blood 25-hydroxyvitamin D levels and the risk of acute lower respiratory tract infection in early childhood. Journal of Tropical Pediatrics. 2013 Feb;59(1):29-35. PMID: 23022743.

175. Moller UK, Streym S, Heickendorff L, et al. Effects of 25OHD concentrations on chances of pregnancy and pregnancy outcomes: a cohort study in healthy Danish women. European Journal of Clinical Nutrition. 2012 Jul;66(7):862-8. PMID: 22378226.

176. Mondul AM, Weinstein SJ, Mannisto S, et al. Serum vitamin D and risk of bladder cancer. Cancer Research. 2010 Nov 15;70(22):9218-23. PMID: 20978193.

177. Mondul AM, Weinstein SJ, Virtamo J, et al. Influence of vitamin D binding protein on the association between circulating vitamin D and risk of bladder cancer. British Journal of Cancer. 2012 Oct 23;107(9):1589-94. PMID: 22990651.

178. Morales E, Guxens M, Llop S, et al. Circulating 25-hydroxyvitamin D3 in pregnancy and infant neuropsychological development. Pediatrics. 2012 Oct;130(4):e913-20. PMID: 22987876.

179. Mueller EA, Seiberling M, Kirch W, et al. Pharmacokinetics and pharmacodynamics of calcium-vitamin D(3) chewable tablets: a single-blind, multiple-dose study in postmenopausal women. Expert Opinion On Drug Metabolism & Toxicology. 2011 Jul;7(7):785-91. PMID: 21635154.

180. Muldowney S, Lucey AJ, Hill TR, et al. Incremental cholecalciferol supplementation up to 15 ug/d throughout winter at 51-55 N has no effect on biomarkers of cardiovascular risk in healthy young and older adults. Journal of Nutrition. 2012 Aug;142(8):1519-25. PMID: 22739371.

181. Mulligan GB, Licata A. Taking vitamin D with the largest meal improves absorption and results in higher serum levels of 25-hydroxyvitamin D. Journal of Bone & Mineral Research. 2010 Apr;25(4):928-30. PMID: 20200983.

182. Naharci I, Bozoglu E, Kocak N, et al. Effect of vitamin D on insulin sensitivity in elderly patients with impaired fasting glucose. Geriatrics & gerontology international. 2012 Jul;12(3):454-60. PMID: 22212745.

183. Nakamura K, Oyama M, Saito T, et al. Nutritional and biochemical parameters associated with 6-year change in bone mineral density in community-dwelling Japanese women aged 69 years and older: The Muramatsu Study. Nutrition. 2012 Apr;28(4):357-61. PMID: 21917422.

184. Naves-Diaz M, Cabezas-Rodriguez I, Barrio-Vazquez S, et al. Low calcidiol levels and risk of progression of aortic calcification. Osteoporosis International. 2012 Mar;23(3):1177-82. PMID: 21308362.

185. Oberhelman SS, Meekins ME, Fischer PR, et al. Maternal Vitamin D Supplementation to Improve the Vitamin D Status of Breast-fed Infants: A Randomized Controlled Trial. Mayo Clinic Proceedings. 2013 Dec;88(12):1378-87. PMID: 24290111.

186. Ojaimi S, Skinner NA, Strauss BJ, et al. Vitamin D deficiency impacts on expression of toll-like receptor-2 and cytokine profile: a pilot study. Journal of Translational Medicine. 2013;11:176. PMID: 23875738.

187. Okazaki R, Sugimoto T, Kaji H, et al. Vitamin D insufficiency defined by serum 25-hydroxyvitamin D and parathyroid hormone before and after oral vitamin D3 load in Japanese subjects. Journal of Bone & Mineral Metabolism. 2011 Jan;29(1):103-10. PMID: 20567864.

188. Ortega RM, Aparicio A, Rodríguez-Rodríguez E, et al. Preliminary data about the influence of vitamin D status on the loss of body fat in young overweight/obese women following two types of hypocaloric diet. The British journal of nutrition; 2008. p. 269-72.

189. Ortega RM, Lopez-Sobaler AM, Aparicio A, et al. Vitamin D status modification by two slightly hypocaloric diets in young overweight/obese women. International Journal for Vitamin & Nutrition Research. 2009 Mar;79(2):71-8. PMID: 20108208.

190. Ostertag A, Cohen-Solal M, Madec Y, et al. Bone changes in spouses having shared lifestyle for 40 years. Joint, Bone, Spine: Revue du Rhumatisme. 2011 May;78(3):285-90. PMID: 20851658.

191. O'Sullivan A, Gibney MJ, Connor AO, et al. Biochemical and metabolomic phenotyping in the identification of a vitamin D responsive metabotype for markers of the metabolic syndrome. Molecular Nutrition & Food Research. 2011 May;55(5):679-90. PMID: 21240901.

192. Parlea L, Bromberg IL, Feig DS, et al. Association between serum 25-hydroxyvitamin D in early pregnancy and risk of gestational diabetes mellitus. Diabetic Medicine. 2012 Jul;29(7):e25-32. PMID: 22150870.

193. Pedone C, Napoli N, Pozzilli P, et al. Quality of diet and potential renal acid load as risk factors for reduced bone density in elderly women. Bone. 2010 Apr;46(4):1063-7. PMID: 20005315.

194. Pekkarinen T, Turpeinen U, Hamalainen E, et al. Serum 25(OH)D3 vitamin status of elderly Finnish women is suboptimal even after summer sunshine but is not associated with bone density or turnover. European Journal of Endocrinology. 2010 Jan;162(1):183-9. PMID: 19841043.

195. Peterson CA, Heffernan ME. Serum tumor necrosis factor-alpha concentrations are negatively correlated with serum 25(OH)D concentrations in healthy women. Journal of Inflammation. 2008;5:10. PMID: 18652680.

196. Pilz S, Frisch S, Koertke H, et al. Effect of vitamin D supplementation on testosterone levels in men. Hormone & Metabolic Research. 2011 Mar;43(3):223-5. PMID: 21154195.

197. Pilz S, van den Hurk K, Nijpels G, et al. Vitamin D status, incident diabetes and prospective changes in glucose metabolism in older subjects: the Hoorn study. Nutrition Metabolism & Cardiovascular Diseases. 2012 Oct;22(10):883-9. PMID: 22673769.

198. Pittas AG, Nelson J, Mitri J, et al. Plasma 25-hydroxyvitamin D and progression to diabetes in patients at risk for diabetes: an ancillary analysis in the Diabetes Prevention Program. Diabetes Care. 2012 Mar;35(3):565-73. PMID: 22323410.

199. Pittas AG, Sun Q, Manson JE, et al. Plasma 25-hydroxyvitamin D concentration and risk of incident type 2 diabetes in women. Diabetes Care. 2010 Sep;33(9):2021-3. PMID: 20805275.

200. Plawecki K, Chapman-Novakofski K. Effectiveness of community intervention in improving bone health behaviors in older adults. Journal of Nutrition in Gerontology & Geriatrics. 2013;32(2):145-60. PMID: 23663213.

201. Pludowski P, Socha P, Karczmarewicz E, et al. Vitamin D supplementation and status in infants: a prospective cohort observational study. Journal of Pediatric Gastroenterology & Nutrition. 2011 Jul;53(1):93-9. PMID: 21694542.

202. Ponda MP, Dowd K, Finkielstein D, et al. The short-term effects of vitamin D repletion on cholesterol: a randomized, placebo-controlled trial. Arteriosclerosis, Thrombosis & Vascular Biology. 2012 Oct;32(10):2510-5. PMID: 22947589.

203. Ponnapakkam T, Bradford E, Gensure R. A treatment trial of vitamin D supplementation in breast-fed infants: universal supplementation is not necessary for rickets prevention in Southern Louisiana. Clinical Pediatrics. 2010 Nov;49(11):1053-60. PMID: 20724336.

204. Porojnicu AC, Moroti-Constantinescu R, Laslau A, et al. Vitamin D status in healthy Romanian caregivers and risk of respiratory infections. Public Health Nutrition. 2012 Nov;15(11):2157-62. PMID: 22414776.

205. Prentice A, Jarjou LMA, Goldberg GR, et al. Maternal plasma 25-hydroxyvitamin D concentration and birthweight, growth and bone mineral accretion of Gambian infants. Acta Paediatrica. 2009 Aug;98(8):1360-2. PMID: 19594476.

206. Principi N, Marchisio P, Terranova L, et al. Impact of vitamin D administration on immunogenicity of trivalent inactivated influenza vaccine in previously unvaccinated children. Human vaccines & Immunotherapeutics. 2013 May;9(5):969-74. PMID: 23324599.

207. Purdue MP, Freedman DM, Gapstur SM, et al. Circulating 25-hydroxyvitamin D and risk of non-hodgkin lymphoma: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. American Journal of Epidemiology. 2010 Jul 1;172(1):58-69. PMID: 20562184.

208. Putman MS, Pitts SA, Milliren CE, et al. A randomized clinical trial of vitamin D supplementation in healthy adolescents. Journal of Adolescent Health. 2013 May;52(5):592-8. PMID: 23608721.

209. Radford LT, Bolland MJ, Gamble GD, et al. Subgroup analysis for the risk of cardiovascular disease with calcium supplements. BoneKEy Reports. 2013;2:293. PMID: 23951541.

210. Rajpathak SN, Xue X, Wassertheil-Smoller S, et al. Effect of 5 y of calcium plus vitamin D supplementation on change in circulating lipids: results from the Women's Health Initiative. American Journal of Clinical Nutrition. 2010 Apr;91(4):894-9. PMID: 20181812.

211. Rejnmark L, Amstrup AK, Mollerup CL, et al. Further insights into the pathogenesis of primary hyperparathyroidism: a nested case-control study. Journal of Clinical Endocrinology & Metabolism. 2013 Jan;98(1):87-96. PMID: 23150677.

212. Rich-Edwards JW, Ganmaa D, Kleinman K, et al. Randomized trial of fortified milk and supplements to raise 25-hydroxyvitamin D concentrations in schoolchildren in Mongolia. The American journal of clinical nutrition; 2011. p. 578-84.

213. Robinson JG, Manson JE, Larson J, et al. Lack of association between 25(OH)D levels and incident type 2 diabetes in older women. Diabetes Care. 2011 Mar;34(3):628-34. PMID: 21289227.

214. Rochat MK, Ege MJ, Plabst D, et al. Maternal vitamin D intake during pregnancy increases gene expression of ILT3 and ILT4 in cord blood. Clinical & Experimental Allergy. 2010 May;40(5):786-94. PMID: 20030662.

215. Rohan TE, Negassa A, Chlebowski RT, et al. A randomized controlled trial of calcium plus vitamin D supplementation and risk of benign proliferative breast disease. Breast Cancer Research & Treatment. 2009 Jul;116(2):339-50. PMID: 18853250.

216. Rosenblum JL, Castro VM, Moore CE, et al. Calcium and vitamin D supplementation is associated with decreased abdominal visceral adipose tissue in overweight and obese adults. American Journal of Clinical Nutrition. 2012 Jan;95(1):101-8. PMID: 22170363.

217. Rossini M, Adami S, Viapiana O, et al. Dose-dependent short-term effects of single high doses of oral vitamin D(3) on bone turnover markers. Calcified Tissue International. 2012 Dec;91(6):365-9. PMID: 23052222.

218. Rossini M, Gatti D, Viapiana O, et al. Short-term effects on bone turnover markers of a single high dose of oral vitamin D3. Journal of Clinical Endocrinology & Metabolism. 2012 Apr;97(4):E622-6. PMID: 22298802.

219. Rossom RC, Espeland MA, Manson JE, et al. Calcium and vitamin D supplementation and cognitive impairment in the women's health initiative. Journal of the American Geriatrics Society. 2012 Dec;60(12):2197-205. PMID: 23176129.

220. Roth DE, Perumal N, Al Mahmud A, et al. Maternal Vitamin D3 Supplementation during the Third Trimester ofPregnancy: Effects on Infant Growth in a Longitudinal Follow-Up StudyinBangladesh. Journal of Pediatrics. 2013 Dec;163(6):1605-11.e3. PMID: 23998516.

221. Saadi HF, Dawodu A, Afandi B, et al. Effect of combined maternal and infant vitamin D supplementation on vitamin D status of exclusively breastfed infants. Maternal & Child Nutrition. 2009 Jan;5(1):25-32. PMID: 19161542.

222. Sahu M, Das V, Aggarwal A, et al. Vitamin D replacement in pregnant women in rural north India: a pilot study. European Journal of Clinical Nutrition. 2009 Sep;63(9):1157-9. PMID: 19455177.

223. Sai AJ, Gallagher JC, Fang X. Effect of hormone therapy and calcitriol on serum lipid profile in postmenopausal older women: association with estrogen receptor- genotypes. Menopause. 2011 Oct;18(10):1101-12. PMID: 21712736.

224. Sakalli H, Arslan D, Yucel AE. The effect of oral and parenteral vitamin D supplementation in the elderly: a prospective, double-blinded, randomized, placebo-controlled study. Rheumatology International. 2012 Aug;32(8):2279-83. PMID: 21556746.

225. Salehpour A, Hosseinpanah F, Shidfar F, et al. A 12-week double-blind randomized clinical trial of vitamin D3 supplementation on body fat mass in healthy overweight and obese women. Nutrition Journal. 2012;11:78. PMID: 22998754.

226. Sanders KM, Stuart AL, Merriman EN, et al. Trials and tribulations of recruiting 2,000 older women onto a clinical trial investigating falls and fractures: Vital D study. BMC Medical Research Methodology. 2009;9:78. PMID: 19930724.

227. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose vitamin D3 and mental well-being: randomised controlled trial. British Journal of Psychiatry. 2011 May;198(5):357-64. PMID: 21525520.

228. Sayers A, Fraser WD, Lawlor DA, et al. 25-Hydroxyvitamin-D3 levels are positively related to subsequent cortical bone development in childhood: findings from a large prospective cohort study. Osteoporosis International. 2012 Aug;23(8):2117-28. PMID: 22080378.

229. Scholl TO, Chen X, Stein P. Maternal vitamin D status and delivery by cesarean. Nutrients. 2012 Apr;4(4):319-30. PMID: 22606373.

230. Schottker B, Herder C, Rothenbacher D, et al. Serum 25-hydroxyvitamin D levels and incident diabetes mellitus type 2: a competing risk analysis in a large population-based cohort of older adults. European Journal of Epidemiology. 2013 Mar;28(3):267-75. PMID: 23354985.

231. Schreuder F, Bernsen RMD, van der Wouden JC. Vitamin D supplementation for nonspecific musculoskeletal pain in non-Western immigrants: a randomized controlled trial. Annals of Family Medicine. 2012 Nov-Dec;10(6):547-55. PMID: 23149532.

232. Seamans KM, Hill TR, Wallace JMW, et al. Cholecalciferol supplementation throughout winter does not affect markers of bone turnover in healthy young and elderly adults. Journal of Nutrition. 2010 Mar;140(3):454-60. PMID: 20089776.

233. Sergi G, Sarti S, Mosele M, et al. Changes in healthy elderly women's physical performance: a 3-year follow-up. Experimental Gerontology. 2011 Nov;46(11):929-33. PMID: 21884781.

234. Shahar DR, Schwarzfuchs D, Fraser D, et al. Dairy calcium intake, serum vitamin D, and successful weight loss. American Journal of Clinical Nutrition. 2010 Nov;92(5):1017-22. PMID: 20810979.

235. Shakiba M, Ghadir M, Nafei Z, et al. Study to evaluate two dosage regimens of vitamin D through an academic year in middle school girls: a randomized trial. Acta Medica Iranica. 2011;49(12):780-3. PMID: 22174164.

236. Shakiba M, Sadr S, Nefei Z, et al. Combination of bolus dose vitamin D with routine vaccination in infants: a randomised trial. Singapore Medical Journal. 2010 May;51(5):440-5. PMID: 20593151.

237. Shapses SA, Sukumar D, Schneider SH, et al. Vitamin D supplementation and calcium absorption during caloric restriction: a randomized double-blind trial. American Journal of Clinical Nutrition. 2013 Mar;97(3):637-45. PMID: 23364004.

238. Shardell M, D'Adamo C, Alley DE, et al. Serum 25-hydroxyvitamin D, transitions between frailty states, and mortality in older adults: the Invecchiare in Chianti Study. Journal of the American Geriatrics Society. 2012 Feb;60(2):256-64. PMID: 22283177.

239. Shipowick CD, Moore CB, Corbett C, et al. Vitamin D and depressive symptoms in women during the winter: a pilot study. Applied Nursing Research. 2009 Aug;22(3):221-5. PMID: 19616172.

240. Shui IM, Mucci LA, Wilson KM, et al. Common genetic variation of the calcium-sensing receptor and lethal prostate cancer risk. Cancer Epidemiology, Biomarkers & Prevention. 2013 Jan;22(1):118-26. PMID: 23125333.

241. Siafarikas A, Piazena H, Feister U, et al. Randomised controlled trial analysing supplementation with 250 versus 500 units of vitamin D3, sun exposure and surrounding factors in breastfed infants. Archives of Disease in Childhood. 2011 Jan;96(1):91-5. PMID: 20861405.

242. Simha V, Mahmood M, Ansari M, et al. Effect of vitamin D replacement on insulin sensitivity in subjects with vitamin D deficiency. Journal of Investigative Medicine. 2012 Dec;60(8):1214-8. PMID: 23111651.

243. Sinha A, Hollingsworth KG, Ball S, et al. Improving the vitamin d status of vitamin d deficient adults is associated with improved mitochondrial oxidative function in skeletal muscle. Journal of Clinical Endocrinology & Metabolism. 2013 Mar;98(3):E509-13. PMID: 23393184.

244. Skaaby T, Husemoen LL, Martinussen T, et al. Vitamin D status, filaggrin genotype, and cardiovascular risk factors: a Mendelian randomization approach. PLoS ONE [Electronic Resource]. 2013;8(2):e57647. PMID: 23460889.

245. Skaaby T, Husemoen LLN, Martinussen T, et al. Vitamin d status, filaggrin genotype, and cardiovascular risk factors: a mendelian randomization approach. PLoS ONE [Electronic Resource]. 2013;8(2):e57647. PMID: 23460889.

246. Skaaby T, Husemoen LLN, Pisinger C, et al. Vitamin D status and changes in cardiovascular risk factors: a prospective study of a general population. Cardiology. 2012;123(1):62-70. PMID: 22986625.

247. Slinin Y, Paudel M, Taylor BC, et al. Association between serum 25(OH) vitamin D and the risk of cognitive decline in older women. Journals of Gerontology Series A-Biological Sciences & Medical Sciences. 2012 Oct;67(10):1092-8. PMID: 22454371.

248. Smith SM, Gardner KK, Locke J, et al. Vitamin D supplementation during Antarctic winter. American Journal of Clinical Nutrition. 2009 Apr;89(4):1092-8. PMID: 19225122.

249. Soares MJ, Chan She Ping-Delfos W. Second meal effects of dietary calcium and vitamin D. European Journal of Clinical Nutrition. 2008 Jul;62(7):872-8. PMID: 17522603.

250. Soares MJ, Chan She Ping-Delfos W, Ghanbari MH. Calcium and vitamin D for obesity: a review of randomized controlled trials. European Journal of Clinical Nutrition. 2011 Sep;65(9):994-1004. PMID: 21731038.

251. Soheilykhah S, Mojibian M, Moghadam MJ, et al. The effect of different doses of vitamin D supplementation on insulin resistance during pregnancy. Gynecological Endocrinology. 2013 Apr;29(4):396-9. PMID: 23350644.

252. Southard EB, Roff A, Fortugno T, et al. Lead, calcium uptake, and related genetic variants in association with renal cell carcinoma risk in a cohort of male Finnish smokers.[Erratum appears in Cancer Epidemiol Biomarkers Prev. 2012 Apr;21(4):696]. Cancer Epidemiology, Biomarkers & Prevention. 2012 Jan;21(1):191-201. PMID: 22086884.

253. Stein MS, Scherer SC, Ladd KS, et al. A randomized controlled trial of high-dose vitamin D2 followed by intranasal insulin in Alzheimer's disease. Journal of Alzheimer's Disease. 2011;26(3):477-84. PMID: 21694461.

254. Stephensen CB, Zerofsky M, Burnett DJ, et al. Ergocalciferol from mushrooms or supplements consumed with a standard meal increases 25-hydroxyergocalciferol but decreases 25-hydroxycholecalciferol in the serum of healthy adults. Journal of Nutrition. 2012 Jul;142(7):1246-52. PMID: 22623385.

255. Sundaram ME, Talbot HK, Zhu Y, et al. Vitamin D is not associated with serologic response to influenza vaccine in adults over 50 years old. Vaccine. 2013 Apr 12;31(16):2057-61. PMID: 23453766.

256. Szulc P, Munoz F, Marchand F, et al. Rapid loss of appendicular skeletal muscle mass is associated with higher all-cause mortality in older men: the prospective MINOS study. American Journal of Clinical Nutrition. 2010 May;91(5):1227-36. PMID: 20237137.

257. Tang JY, Fu T, Leblanc E, et al. Calcium plus vitamin D supplementation and the risk of nonmelanoma and melanoma skin cancer: post hoc analyses of the women's health initiative randomized controlled trial. Journal of Clinical Oncology. 2011 Aug 1;29(22):3078-84. PMID: 21709199.

258. Tang JY, Parimi N, Wu A, et al. Inverse association between serum 25(OH) vitamin D levels and non-melanoma skin cancer in elderly men. Cancer Causes & Control. 2010 Mar;21(3):387-91. PMID: 19921445.

259. Tolppanen A-M, Sayers A, Fraser WD, et al. Association of serum 25-hydroxyvitamin D3 and D2 with academic performance in childhood: findings from a prospective birth cohort. Journal of Epidemiology & Community Health. 2012 Dec;66(12):1137-42. PMID: 22493513.

260. Tolppanen A-M, Sayers A, Fraser WD, et al. The association of 25-hydroxyvitamin D3 and D2 with behavioural problems in childhood. PLoS ONE [Electronic Resource]. 2012;7(7):e40097. PMID: 22808099.

261. Tolppanen A-M, Sayers A, Fraser WD, et al. The association of serum 25-hydroxyvitamin D3 and D2 with depressive symptoms in childhood--a prospective cohort study. Journal of Child Psychology & Psychiatry & Allied Disciplines. 2012 Jul;53(7):757-66. PMID: 22211693.

262. Tolppanen A-M, Sayers A, Fraser WD, et al. Serum 25-hydroxyvitamin D3 and D2 and non-clinical psychotic experiences in childhood. PLoS ONE [Electronic Resource]. 2012;7(7):e41575. PMID: 22848531.

263. Toriola AT, Surcel H-M, Agborsangaya C, et al. Serum 25-hydroxyvitamin D and the risk of ovarian cancer. European Journal of Cancer. 2010 Jan;46(2):364-9. PMID: 19713101.

264. Toriola AT, Surcel H-M, Calypse A, et al. Independent and joint effects of serum 25-hydroxyvitamin D and calcium on ovarian cancer risk: a prospective nested case-control study. European Journal of Cancer. 2010 Oct;46(15):2799-805. PMID: 20601305.

265. Toss G, Magnusson P. Is a daily supplementation with 40 microgram vitamin D3 sufficient? A randomised controlled trial. European Journal of Nutrition. 2012 Dec;51(8):939-45. PMID: 22086300.

266. Tran B, Armstrong BK, Ebeling PR, et al. Effect of vitamin D supplementation on antibiotic use: a randomized controlled trial. American Journal of Clinical Nutrition. 2014 Jan;99(1):156-61. PMID: 24108783.

267. Trilok-Kumar G, Arora H, Rajput M, et al. Effect of vitamin D supplementation of low birth weight term Indian infants from birth on cytokine production at 6 months. European Journal of Clinical Nutrition. 2012 Jun;66(6):746-50. PMID: 22510791.

268. Trummer O, Pilz S, Hoffmann MM, et al. Vitamin D and mortality: a Mendelian randomization study. Clinical Chemistry. 2013 May;59(5):793-7. PMID: 23319826.

269. Tzotzas T, Papadopoulou FG, Tziomalos K, et al. Rising serum 25-hydroxy-vitamin D levels after weight loss in obese women correlate with improvement in insulin resistance. Journal of Clinical Endocrinology & Metabolism. 2010 Sep;95(9):4251-7. PMID: 20534751.

270. Umhau JC, George DT, Heaney RP, et al. Low vitamin D status and suicide: a case-control study of active duty military service members. PLoS ONE [Electronic Resource]. 2013;8(1):e51543. PMID: 23308099.

271. Urbain P, Singler F, Ihorst G, et al. Bioavailability of vitamin D2 from UV-B-irradiated button mushrooms in healthy adults deficient in serum 25-hydroxyvitamin D: a randomized controlled trial. European Journal of Clinical Nutrition. 2011 Aug;65(8):965-71. PMID: 21540874.

272. van Ballegooijen AJ, Snijder MB, Visser M, et al. Vitamin D in relation to myocardial structure and function after eight years of follow-up: the Hoorn study. Annals of Nutrition & Metabolism. 2012;60(1):69-77. PMID: 22343754.

273. van den Berg G, van Eijsden M, Vrijkotte TG, et al. Suboptimal maternal vitamin D status and low education level as determinants of small-for-gestational-age birth weight. European Journal of Nutrition. 2013 Feb;52(1):273-9. PMID: 22350924.

274. van der Pols JC, Russell A, Bauer U, et al. Vitamin D status and skin cancer risk independent of time outdoors: 11-year prospective study in an Australian community. Journal of Investigative Dermatology. 2013 Mar;133(3):637-41. PMID: 23076499.

275. Viljakainen HT, Korhonen T, Hytinantti T, et al. Maternal vitamin D status affects bone growth in early childhood--a prospective cohort study. Osteoporosis International. 2011 Mar;22(3):883-91. PMID: 21153404.

276. Viljakainen HT, Vaisanen M, Kemi V, et al. Wintertime vitamin D supplementation inhibits seasonal variation of calcitropic hormones and maintains bone turnover in healthy men. Journal of Bone & Mineral Research. 2009 Feb;24(2):346-52. PMID: 18847321.

277. Villamor E, Marin C, Mora-Plazas M, et al. Vitamin D deficiency and age at menarche: a prospective study. American Journal of Clinical Nutrition. 2011 Oct;94(4):1020-5. PMID: 21831989.

278. von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient—a randomised, placebo-controlled trial. British Journal of Nutrition. 2010 Feb;103(4):549-55. PMID: 19781131.

279. von Hurst PR, Stonehouse W, Kruger MC, et al. Vitamin D supplementation suppresses age-induced bone turnover in older women who are vitamin D deficient. Journal of Steroid Biochemistry & Molecular Biology. 2010 Jul;121(1-2):293-6. PMID: 20304051.

280. Wagner CL, Howard C, Hulsey TC, et al. Circulating 25-Hydroxy-Vitamin D (25-OH-D) Levels in Fully Breastfed Infants on Oral Vitamin D (VitD) Supplementation. Pediatric Academic Societies Annual Meeting; 2009 May 2 5; Baltimore MD, United States; 2009.

281. Wagner CL, Howard C, Hulsey TC, et al. Circulating 25-hydroxyvitamin d levels in fully breastfed infants on oral vitamin d supplementation. International Journal of Endocrinology Print. 2010;2010:235035. PMID: 20049156.

282. Wagner CL, McNeil R, Hamilton SA, et al. A randomized trial of vitamin D supplementation in 2 community health center networks in South Carolina. American Journal of Obstetrics & Gynecology. 2013 Feb;208(2):137.e1-13. PMID: 23131462.

283. Wagner D, Sidhom G, Whiting SJ, et al. The bioavailability of vitamin D from fortified cheeses and supplements is equivalent in adults. Journal of Nutrition. 2008 Jul;138(7):1365-71. PMID: 18567762.

284. Walsh JM, Kilbane M, McGowan CA, et al. Pregnancy in dark winters: implications for fetal bone growth? Fertility & Sterility. 2013 Jan;99(1):206-11. PMID: 23040526.

285. Walsh JM, McGowan CA, Kilbane M, et al. The relationship between maternal and fetal vitamin D, insulin resistance, and fetal growth. Reproductive Sciences. 2013 May;20(5):536-41. PMID: 22968764.

286. Wang JB, Abnet CC, Chen W, et al. Association between serum 25(OH) vitamin D, incident liver cancer and chronic liver disease mortality in the Linxian Nutrition Intervention Trials: a nested case-control study. British Journal of Cancer. 2013 Oct 1;109(7):1997-2004. PMID: 24008664.

287. Wang O, Nie M, Hu YY, et al. Association between vitamin D insufficiency and the risk for gestational diabetes mellitus in pregnant Chinese women. Biomedical & Environmental Sciences. 2012 Aug;25(4):399-406. PMID: 23026519.

288. Weinstein SJ, Mondul AM, Kopp W, et al. Circulating 25-hydroxyvitamin D, vitamin D-binding protein and risk of prostate cancer. International Journal of Cancer. 2013 Jun 15;132(12):2940-7. PMID: 23180681.

289. Weinstein SJ, Yu K, Horst RL, et al. Serum 25-hydroxyvitamin D and risk of lung cancer in male smokers: a nested case-control study. PLoS ONE [Electronic Resource]. 2011;6(6):e20796. PMID: 21695165.

290. Williams DM, Fraser A, Fraser WD, et al. Associations of maternal 25-hydroxyvitamin D in pregnancy with offspring cardiovascular risk factors in childhood and adolescence: findings from the Avon Longitudinal Study of Parents and Children. Heart. 2013 Dec;99(24):1849-56. PMID: 24125739.

291. Young BE, McNanley TJ, Cooper EM, et al. Maternal vitamin D status and calcium intake interact to affect fetal skeletal growth in utero in pregnant adolescents. American Journal of Clinical Nutrition. 2012 May;95(5):1103-12. PMID: 22492380.

292. Young KA, Engelman CD, Langefeld CD, et al. Association of plasma vitamin D levels with adiposity in Hispanic and African Americans. Journal of Clinical Endocrinology & Metabolism. 2009 Sep;94(9):3306-13. PMID: 19549738.

293. Yu CKH, Ertl R, Skyfta E, et al. Maternal serum vitamin D levels at 11-13 weeks of gestation in preeclampsia. Journal of Human Hypertension. 2013 Feb;27(2):115-8. PMID: 22336906.

294. Yu CKH, Sykes L, Sethi M, et al. Vitamin D deficiency and supplementation during pregnancy. Clinical Endocrinology. 2009 May;70(5):685-90. PMID: 18771564.

295. Yusupov E, Li-Ng M, Pollack S, et al. Vitamin d and serum cytokines in a randomized clinical trial. International Journal of Endocrinology Print. 2010PMID: 20871847.

296. Zeleniuch-Jacquotte A, Gallicchio L, Hartmuller V, et al. Circulating 25-hydroxyvitamin D and risk of endometrial cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. American Journal of Epidemiology. 2010 Jul 1;172(1):36-46. PMID: 20562189.

297. Zgaga L, Agakov F, Theodoratou E, et al. Model selection approach suggests causal association between 25-hydroxyvitamin D and colorectal cancer. PLoS ONE [Electronic Resource]. 2013;8(5):e63475. PMID: 23717431.

298. Zhang C, Qiu C, Hu FB, et al. Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus. PLoS ONE [Electronic Resource]. 2008;3(11):e3753. PMID: 19015731.

299. Zhang LR, Sawka AM, Adams L, et al. Vitamin and mineral supplements and thyroid cancer: a systematic review. European Journal of Cancer Prevention. 2013 Mar;22(2):158-68. PMID: 22926510.

300. Zhao L-J, Zhou Y, Bu F, et al. Factors predicting vitamin D response variation in non-Hispanic white postmenopausal women. Journal of Clinical Endocrinology & Metabolism. 2012 Aug;97(8):2699-705. PMID: 22585090.

301. Zheng W, Danforth KN, Tworoger SS, et al. Circulating 25-hydroxyvitamin D and risk of epithelial ovarian cancer: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. American Journal of Epidemiology. 2010 Jul 1;172(1):70-80. PMID: 20562186.

302. Zhou J, Zhao L-J, Watson P, et al. The effect of calcium and vitamin D supplementation on obesity in postmenopausal women: secondary analysis for a large-scale, placebo controlled, double-blind, 4-year longitudinal clinical trial. Nutrition & Metabolism. 2010;7:62. PMID: 20650013.

303. Zhou JC, Zhu YM, Guo P, et al. Serum 25(OH)D and Lipid Levels in Chinese Obese and Normal Weight Males before and after Oral Vitamin D Supplementation. Biomedical & Environmental Sciences. 2013 Oct;26(10):801-7. PMID: 24215874.

304. Zhu H, Guo D, Li K, et al. Increased telomerase activity and vitamin D supplementation in overweight African Americans. International Journal of Obesity. 2012 Jun;36(6):805-9. PMID: 21986705.

305. Zittermann A, von Helden R, Grant W, et al. An estimate of the survival benefit of improving vitamin D status in the adult german population. Dermato-endocrinology. 2009 Nov;1(6):300-6. PMID: 21572875.

306. Zwart SR, Parsons H, Kimlin M, et al. A 250mug/week dose of vitamin D was as effective as a 50mug/d dose in healthy adults, but a regimen of four weekly followed by monthly doses of 1250mug raised the risk of hypercalciuria. British Journal of Nutrition. 2013 Nov;110(10):1866-72. PMID: 23595003.

Duration Not of Interest—N=10

1. Abrams SA, Hawthorne KM, Rogers SP, et al. Effects of ethnicity and vitamin D supplementation on vitamin D status and changes in bone mineral content in infants. BMC Pediatrics. 2012;12:6. PMID: 22248486.

2. Barker T, Martins TB, Hill HR, et al. Different doses of supplemental vitamin D maintain interleukin-5 without altering skeletal muscle strength: a randomized, double-blind, placebo-controlled study in vitamin D sufficient adults. Nutrition & Metabolism. 2012;9(1):16. PMID: 22405472.

3. Carrillo AE, Flynn MG, Pinkston C, et al. Impact of vitamin D supplementation during a resistance training intervention onbody composition, muscle function, and glucose tolerance in overweight andobese adults. Clinical Nutrition. 2013 Jun;32(3):375-81. PMID: 23034474.

4. Close GL, Leckey J, Patterson M, et al. The effects of vitamin D(3) supplementation on serum total 25[OH]D concentration and physical performance: a randomised dose-response study. British Journal of Sports Medicine. 2013 Jul;47(11):692-6. PMID: 23410885.

5. Diogenes ME, Bezerra FF, Rezende EP, et al. Effect of calcium plus vitamin D supplementation during pregnancy in Brazilian adolescent mothers: a randomized, placebo-controlled trial. American Journal of Clinical Nutrition. 2013 Jul;98(1):82-91. PMID: 23719547.

6. Gallo S, Comeau K, Vanstone C, et al. Effect of different dosages of oral vitamin D supplementation on vitamin D status in healthy, breastfed infants: a randomized trial. JAMA. 2013 May 1;309(17):1785-92. PMID: 23632722.

7. Lagari V, Gomez-Marin O, Levis S. The role of vitamin D in improving physical performance in the elderly. Journal of Bone & Mineral Research. 2013 Oct;28(10):2194-201. PMID: 23553992.

8. Nieman DC, Gillitt ND, Shanely RA, et al. Vitamin D2 Supplementation Amplifies Eccentric Exercise-Induced Muscle Damage in NASCAR Pit Crew Athletes. Nutrients. 2013;6(1):63-75. PMID: 24362707.

9. Wamberg L, Pedersen SB, Richelsen B, et al. The effect of high-dose vitamin d supplementation on calciotropic hormones and bone mineral density in obese subjects with low levels of circulating 25-hydroxyvitamin d: results from a randomized controlled study. Calcified Tissue International. 2013 Jul;93(1):69-77. PMID: 23591713.

10. Wyon MA, Koutedakis Y, Wolman R, et al. The influence of winter vitamin D supplementation on muscle function and injury occurrence in elite ballet dancers: A controlled study. Journal of Science & Medicine in Sport. 2014 Jan;17(1):8-12. PMID: 23619160.

Duplicate Data—N=2

1. Al-Shaar L, Nabulsi M, Maalouf J, et al. Effect of vitamin D replacement on hip structural geometry in adolescents: a randomized controlled trial. Bone. 2013 Oct;56(2):296-303. PMID: 23810841.

2. Kukuljan S, Nowson CA, Bass SL, et al. Effects of a multi-component exercise program and calcium-vitamin-D3-fortified milk on bone mineral density in older men: a randomised controlled trial. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA; 2009. p. 1241-51.

Systematic Review Excludes- N=169

1. Aghajafari F, Nagulesapillai T, Ronksley PE, et al. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. BMJ. 2013;346:f1169. PMID: 23533188.

2. Aghajafari F, Nagulesapillai T, Ronksley PE, et al. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies (Provisional abstract). Bmj; 2013. p. f1169.

3. Anglin RES, Samaan Z, Walter SD, et al. Vitamin D deficiency and depression in adults: systematic review and meta-analysis. British Journal of Psychiatry. 2013 Feb;202:100-7. PMID: 23377209.

4. Annweiler C, Allali G, Allain P, et al. Vitamin D and cognitive performance in adults: a systematic review. European Journal of Neurology. 2009 Oct;16(10):1083-9. PMID: 19659751.

5. Annweiler C, Llewellyn DJ, Beauchet O. Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis. Journal of Alzheimer's Disease. 2013;33(3):659-74. PMID: 23042216.

6. Annweiler C, Schott AM, Berrut G, et al. Vitamin D-related changes in physical performance: a systematic review. Journal of Nutrition, Health & Aging. 2009 Dec;13(10):893-8. PMID: 19924350.

7. Antico A, Tampoia M, Tozzoli R, et al. Can supplementation with vitamin D reduce the risk or modify the course of autoimmune diseases? A systematic review of the literature. Autoimmunity Reviews. 2012 Dec;12(2):127-36. PMID: 22776787.

8. Autier P, Boniol M, Pizot C, et al. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol. 2014;2:76-89.

9. Avenell A, Gillespie WJ, Gillespie LD, et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database of Systematic Reviews. 2009(2):CD000227. PMID: 19370554.

10. Bagnoli F, Casucci M, Toti S, et al. Is vitamin D supplementation necessary in healthy full-term breastfed infants? A follow-up study of bone mineralization in healthy full-term infants with and without supplemental vitamin D. Minerva Pediatrica. 2013 Jun;65(3):253-60. PMID: 23685376.

11. Bailey EE, Ference EH, Alikhan A, et al. Combination treatments for psoriasis: a systematic review and meta-analysis. Archives of Dermatology. 2012 Apr;148(4):511-22. PMID: 22184718.

12. Balion C, Griffith LE, Strifler L, et al. Vitamin D, cognition, and dementia: a systematic review and meta-analysis. Neurology. 2012 Sep 25;79(13):1397-405. PMID: 23008220.

13. Balzer K, Bremer M, Schramm S, et al. Falls prevention for the elderly. GMS Health Technology Assessment. 2012;8:Doc01. PMID: 22536299.

14. Barengolts E. Vitamin D role and use in prediabetes. Endocrine Practice. 2010 May-Jun;16(3):476-85. PMID: 20150028.

15. Bassil D, Rahme M, Hoteit M, et al. Hypovitaminosis D in the Middle East and North Africa: Prevalence, risk factors and impact on outcomes. Dermato-endocrinology. 2013 Apr 1;5(2):274-98. PMID: 24194968.

16. Bauer SR, Hankinson SE, Bertone-Johnson ER, et al. Plasma vitamin D levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies. Medicine. 2013 May;92(3):123-31. PMID: 23625163.

17. Bergman GJD, Fan T, McFetridge JT, et al. Efficacy of vitamin D3 supplementation in preventing fractures in elderly women: a meta-analysis. Current Medical Research & Opinion. 2010 May;26(5):1193-201. PMID: 20302551.

18. Bergman P, Lindh AU, Bjorkhem-Bergman L, et al. Vitamin D and respiratory tract infections: a systematic review and meta-analysis of randomized controlled trials (Provisional abstract). Database of Abstracts of Reviews of Effects; 2013. p. e65835.

19. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ. 2009;339:b3692. PMID: 19797342.

20. Bischoff-Ferrari HA, Willett WC, Orav EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention.[Erratum appears in N Engl J Med. 2012 Aug 2;367(5):481 Note: Oray, Endel J [corrected to Orav, Endel J]]. New England Journal of Medicine. 2012 Jul 5;367(1):40-9. PMID: 22762317.

21. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: a meta-analysis of randomized controlled trials. Archives of Internal Medicine. 2009 Mar 23;169(6):551-61. PMID: 19307517.

22. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database of Systematic Reviews. 2011(7):CD007470. PMID: 21735411.

23. Black LJ, Seamans KM, Cashman KD, et al. An updated systematic review and meta-analysis of the efficacy of vitamin D food fortification. Journal of Nutrition. 2012 Jun;142(6):1102-8. PMID: 22513988.

24. Bouillon R, Van Schoor NM, Gielen E, et al. Optimal vitamin D status: a critical analysis on the basis of evidence-based medicine. Journal of Clinical Endocrinology & Metabolism. 2013 Aug;98(8):E1283-304. PMID: 23922354.

25. Brandao CMR, Lima MG, Silva ALd, et al. Treatment of postmenopausal osteoporosis in women: a systematic review. Cadernos de Saude Publica. 2008;24 Suppl 4:s592-606. PMID: 18797733.

26. Burgaz A, Orsini N, Larsson SC, et al. Blood 25-hydroxyvitamin D concentration and hypertension: a meta-analysis. Journal of Hypertension. 2011 Apr;29(4):636-45. PMID: 21191311.

27. Cameron ID, Gillespie LD, Robertson MC, et al. Interventions for preventing falls in older people in care facilities and hospitals. Cochrane Database of Systematic Reviews. 2012;12:CD005465. PMID: 23235623.

28. Cameron ID, Murray GR, Gillespie LD, et al. Interventions for preventing falls in older people in nursing care facilities and hospitals. Cochrane Database of Systematic Reviews. 2010(1):CD005465. PMID: 20091578.

29. Cao Y, Winzenberg T, Nguo K, et al. Association between serum levels of 25-hydroxyvitamin D and osteoarthritis: a systematic review (Provisional abstract). Database of Abstracts of Reviews of Effects; 2013. p. 1323-34.

30. Cao Y, Winzenberg T, Nguo K, et al. Association between serum levels of 25-hydroxyvitamin D and osteoarthritis: a systematic review. Rheumatology. 2013 Jul;52(7):1323-34. PMID: 23542678.

31. Carroll C, Cooper K, Papaioannou D, et al. Supplemental calcium in the chemoprevention of colorectal cancer: a systematic review and meta-analysis. Clinical Therapeutics. 2010 May;32(5):789-803. PMID: 20685491.

32. Cashman KD, Fitzgerald AP, Kiely M, et al. A systematic review and meta-regression analysis of the vitamin D intake-serum 25-hydroxyvitamin D relationship to inform European recommendations. British Journal of Nutrition. 2011 Dec;106(11):1638-48. PMID: 22000709.

33. Charan J, Goyal JP, Saxena D, et al. Vitamin D for prevention of respiratory tract infections: A systematic review and meta-analysis. Journal of Pharmacology & Pharmacotherapeutics. 2012 Oct;3(4):300-3. PMID: 23326099.

34. Chowdhury R, Stevens S, Ward H, et al. Circulating vitamin D, calcium and risk of cerebrovascular disease: a systematic review and meta-analysis. European Journal of Epidemiology. 2012 Aug;27(8):581-91. PMID: 22961293.

35. Christesen HT, Elvander C, Lamont RF, et al. The impact of vitamin D in pregnancy on extraskeletal health in children: a systematic review. Acta Obstetricia et Gynecologica Scandinavica. 2012 Dec;91(12):1368-80. PMID: 23210535.

36. Christesen HT, Falkenberg T, Lamont RF, et al. The impact of vitamin D on pregnancy: a systematic review. Acta Obstetricia et Gynecologica Scandinavica. 2012 Dec;91(12):1357-67. PMID: 22974137.

37. Chua GT, Wong RY. Association Between Vitamin D Dosing Regimen and Fall Prevention in Long-term Care Seniors. Canadian Geriatrics Journal CGJ. 2011 Dec;14(4):93-9. PMID: 23251320.

38. Chung M, Balk EM, Brendel M, et al. Vitamin D and calcium: a systematic review of health outcomes. Evidence Report/Technology Assessment. 2009 Aug(183):1-420. PMID: 20629479.

39. Chung M, Lee J, Terasawa T, et al. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Annals of Internal Medicine. 2011 Dec 20;155(12):827-38. PMID: 22184690.

40. Church J, Goodall S, Norman R, et al. An economic evaluation of community and residential aged care falls prevention strategies in NSW. New South Wales Public Health Bulletin. 2011 Jun;22(3-4):60-8. PMID: 21632001.

41. Cook LS, Neilson HK, Lorenzetti DL, et al. A systematic literature review of vitamin D and ovarian cancer. American Journal of Obstetrics & Gynecology. 2010 Jul;203(1):70.e1-8. PMID: 20227054.

42. Cooper C, Reginster JY, Cortet B, et al. Long-term treatment of osteoporosis in postmenopausal women: a review from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF). Current Medical Research & Opinion. 2012 Mar;28(3):475-91. PMID: 22356102.

43. Cooper K, Squires H, Carroll C, et al. Chemoprevention of colorectal cancer: systematic review and economic evaluation. Health Technology Assessment (Winchester, England). 2010 Jun;14(32):1-206. PMID: 20594533.

44. De-Regil LM, Palacios C, Ansary A, et al. Vitamin D supplementation for women during pregnancy. Cochrane Database of Systematic Reviews. 2012;2:CD008873. PMID: 22336854.

45. Dolinsky DH, Armstrong S, Mangarelli C, et al. The association between vitamin d and cardiometabolic risk factors in children: a systematic review. Clinical Pediatrics. 2013 Mar;52(3):210-23. PMID: 23299837.

46. Dong JY, Zhang WG, Chen JJ, et al. Vitamin D intake and risk of type 1 diabetes: a meta-analysis of observational studies. Nutrients. 2013 Sep;5(9):3551-62. PMID: 24036529.

47. Elamin MB, Abu Elnour NO, Elamin KB, et al. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. Journal of Clinical Endocrinology & Metabolism. 2011 Jul;96(7):1931-42. PMID: 21677037.

48. Etgen T, Sander D, Bickel H, et al. Mild cognitive impairment and dementia: the importance of modifiable risk factors. Deutsches Arzteblatt International. 2011 Nov;108(44):743-50. PMID: 22163250.

49. Etgen T, Sander D, Bickel H, et al. Vitamin D deficiency, cognitive impairment and dementia: a systematic review and meta-analysis. Dementia & Geriatric Cognitive Disorders. 2012;33(5):297-305. PMID: 22759681.

50. Feneis JF, Arora RR. Role of vitamin D in blood pressure homeostasis. American Journal of Therapeutics. 2010 Nov-Dec;17(6):e221-9. PMID: 20216204.

51. Forte A, De Sanctis R, Leonetti G, et al. Dietary chemoprevention of colorectal cancer. Annali Italiani di Chirurgia. 2008 Jul-Aug;79(4):261-7. PMID: 19093628.

52. Fosnight SM, Zafirau WJ, Hazelett SE. Vitamin D supplementation to prevent falls in the elderly: evidence and practical considerations. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy. 2008 Feb;28(2):225-34. PMID: 18225968.

53. Gandini S, Boniol M, Haukka J, et al. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. International Journal of Cancer. 2011 Mar 15;128(6):1414-24. PMID: 20473927.

54. Gates BJ, Sonnett TE, Duvall CAK, et al. Review of osteoporosis pharmacotherapy for geriatric patients. American Journal of Geriatric Pharmacotherapy. 2009 Dec;7(6):293-323. PMID: 20129253.

55. George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. Diabetic Medicine. 2012 Aug;29(8):e142-50. PMID: 22486204.

56. Gilbert R, Martin RM, Beynon R, et al. Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose-response meta-analysis. Cancer Causes & Control. 2011 Mar;22(3):319-40. PMID: 21203822.

57. Gillespie LD, Gillespie WJ, Robertson MC, et al. WITHDRAWN: Interventions for preventing falls in elderly people. Cochrane Database of Systematic Reviews. 2009(2):CD000340. PMID: 19370556.

58. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database of Systematic Reviews. 2009(2):CD007146. PMID: 19370674.

59. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Cochrane Database of Systematic Reviews. 2012;9:CD007146. PMID: 22972103.

60. Gissel T, Rejnmark L, Mosekilde L, et al. Intake of vitamin D and risk of breast cancer--a meta-analysis. Journal of Steroid Biochemistry & Molecular Biology. 2008 Sep;111(3-5):195-9. PMID: 18590821.

61. Grandi NC, Breitling LP, Brenner H. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. Preventive Medicine. 2010 Sep-Oct;51(3-4):228-33. PMID: 20600257.

62. Grant WB. Relation between prediagnostic serum 25-hydroxyvitamin D level and incidence of breast, colorectal, and other cancers. Journal of Photochemistry & Photobiology. B—Biology. 2010 Nov 3;101(2):130-6. PMID: 20570169.

63. Group D. Patient level pooled analysis of 68 500 patients from seven major vitamin D fracture trials in US and Europe. BMJ. 2010;340:b5463. PMID: 20068257.

64. Gustafson CJ, Watkins C, Hix E, et al. Combination therapy in psoriasis: an evidence-based review. American Journal of Clinical Dermatology. 2013 Feb;14(1):9-25. PMID: 23329077.

65. Haentjens P, Vanderschueren D, Lips P, et al. Need for additional calcium to reduce the risk of hip or any nonvertebral fracture with vitamin D supplementation: evidence from a comparative meta-analysis of randomized controlled trials. The Journal of Bone and Joint Surgery (Proceedings); 2009. p. 98.

66. Health Quality O. Prevention of falls and fall-related injuries in community-dwelling seniors: an evidence-based analysis. Ontario Health Technology Assessment Series. 2008;8(2):1-78. PMID: 23074507.

67. Helzlsouer KJ, Committee VS. Overview of the Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. American Journal of Epidemiology. 2010 Jul 1;172(1):4-9. PMID: 20562193.

68. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. Mayo Clinic Proceedings. 2013 Jul;88(7):720-55. PMID: 23790560.

69. Hujoel PP. Vitamin D and dental caries in controlled clinical trials: systematic review and meta-analysis. Nutrition Reviews. 2013 Feb;71(2):88-97. PMID: 23356636.

70. Hujoel PP. Vitamin D and dental caries in controlled clinical trials: systematic review and meta-analysis (Structured abstract). Database of Abstracts of Reviews of Effects; 2013. p. 88-97.

71. Huncharek M, Muscat J, Kupelnick B. Impact of dairy products and dietary calcium on bone-mineral content in children: results of a meta-analysis. Bone. 2008 Aug;43(2):312-21. PMID: 18539555.

72. Huncharek M, Muscat J, Kupelnick B. Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer: a meta-analysis of 26,769 cases from 45 observational studies. Nutrition & Cancer. 2008;60(4):421-41. PMID: 18584476.

73. Ingraham BA, Bragdon B, Nohe A. Molecular basis of the potential of vitamin D to prevent cancer. Current Medical Research & Opinion. 2008 Jan;24(1):139-49. PMID: 18034918.

74. Jolliffe DA, Griffiths CJ, Martineau AR. Vitamin D in the prevention of acute respiratory infection: systematic review of clinical studies. Journal of Steroid Biochemistry & Molecular Biology. 2013 Jul;136:321-9. PMID: 23220552.

75. Ju SY, Lee YJ, Jeong SN. Serum 25-hydroxyvitamin D levels and the risk of depression: a systematic review and meta-analysis. Journal of Nutrition, Health & Aging. 2013;17(5):447-55. PMID: 23636546.

76. Kalyani RR, Stein B, Valiyil R, et al. Vitamin D treatment for the prevention of falls in older adults: systematic review and meta-analysis. Journal of the American Geriatrics Society. 2010 Jul;58(7):1299-310. PMID: 20579169.

77. Khan H, Kunutsor S, Franco OH, et al. Vitamin D, type 2 diabetes and other metabolic outcomes: a systematic review and meta-analysis of prospective studies. Proceedings of the Nutrition Society. 2013 Feb;72(1):89-97. PMID: 23107484.

78. Kunutsor SK, Apekey TA, Steur M. Vitamin D and risk of future hypertension: meta-analysis of 283,537 participants. European Journal of Epidemiology. 2013 Mar;28(3):205-21. PMID: 23456138.

79. Kunutsor SK, Apekey TA, Steur M. Vitamin D and risk of future hypertension: meta-analysis of 283,537 participants (Provisional abstract). Database of Abstracts of Reviews of Effects; 2013. p. 205-21.

80. Lai JKC, Lucas RM, Clements MS, et al. Hip fracture risk in relation to vitamin D supplementation and serum 25-hydroxyvitamin D levels: a systematic review and meta-analysis of randomised controlled trials and observational studies. BMC Public Health. 2010;10:331. PMID: 20540727.

81. Lamberg-Allardt C, Brustad M, Meyer HE, et al. Vitamin D—a systematic literature review for the 5th edition of the Nordic Nutrition Recommendations. Food & Nutrition Research. 2013;57PMID: 24106457.

82. Lazzeroni M, Serrano D, Pilz S, et al. Vitamin d supplementation and cancer: review of randomized controlled trials. Current Medicinal Chemistry—Anti-Cancer Agents. 2013 Jan 1;13(1):118-25. PMID: 23094929.

83. Lee JE. Circulating levels of vitamin D, vitamin D receptor polymorphisms, and colorectal adenoma: a meta-analysis. Nutrition Research & Practice. 2011 Oct;5(5):464-70. PMID: 22125685.

84. Liu SL, Zhao YP, Dai MH, et al. Vitamin D status and the risk of pancreatic cancer: a meta-analysis. Chinese Medical Journal. 2013;126(17):3356-9. PMID: 24033964.

85. Liu ZM, Woo J, Wu SH, et al. The role of vitamin D in blood pressure, endothelial and renal function in postmenopausal women. Nutrients. 2013 Jul;5(7):2590-610. PMID: 23839167.

86. Ma Y, Zhang P, Wang F, et al. Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. Journal of Clinical Oncology. 2011 Oct 1;29(28):3775-82. PMID: 21876081.

87. MacLean C, Newberry S, Maglione M, et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. Annals of Internal Medicine. 2008 Feb 5;148(3):197-213. PMID: 18087050.

88. Mahomed K, Gulmezoglu AM. WITHDRAWN: Vitamin D supplementation in pregnancy. Cochrane Database of Systematic Reviews. 2011(2):CD000228. PMID: 21328247.

89. Mao PJ, Zhang C, Tang L, et al. Effect of calcium or vitamin D supplementation on vascular outcomes: A meta-analysis of randomized controlled trials. International Journal of Cardiology. 2013 Oct 30;169(2):106-11. PMID: 24035175.

90. Mao S, Huang S. Vitamin D supplementation and risk of respiratory tract infections: a meta-analysis of randomized controlled trials. Scandinavian Journal of Infectious Diseases. 2013 Sep;45(9):696-702. PMID: 23815596.

91. Marik PE, Flemmer M. Do dietary supplements have beneficial health effects in industrialized nations: what is the evidence? Jpen: Journal of Parenteral & Enteral Nutrition. 2012 Mar;36(2):159-68. PMID: 22275325.

92. Melek J, Sakuraba A. Efficacy and Safety of Medical Therapy for Low Bone Mineral Density in Patients With Inflammatory Bowel Disease: A Meta-analysis and Systematic Review. Clinical Gastroenterology & Hepatology. 2014 Jan;12(1):32-44.e5. PMID: 23981521.

93. Michael YL, Whitlock EP, Lin JS, et al. Primary care-relevant interventions to prevent falling in older adults: a systematic evidence review for the U.S. Preventive Services Task Force. Annals of Internal Medicine. 2010 Dec 21;153(12):815-25. PMID: 21173416.

94. Miller PD. Vitamin D, calcium, and cardiovascular mortality: a perspective from a plenary lecture given at the annual meeting of the American Association of Clinical Endocrinologists. Endocrine Practice. 2011 Sep-Oct;17(5):798-806. PMID: 21856593.

95. Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. European Journal of Clinical Nutrition. 2011 Sep;65(9):1005-15. PMID: 21731035.

96. Mohr SB, Gorham ED, Alcaraz JE, et al. Serum 25-hydroxyvitamin D and prevention of breast cancer: pooled analysis.[Erratum appears in Anticancer Res. 2011 Oct;31(10):3637]. Anticancer Research. 2011 Sep;31(9):2939-48. PMID: 21868542.

97. Morse NL. Benefits of docosahexaenoic acid, folic acid, vitamin D and iodine on foetal and infant brain development and function following maternal supplementation during pregnancy and lactation. Nutrients. 2012 Jul;4(7):799-840. PMID: 22852064.

98. Mouli VP, Ananthakrishnan AN. Review article: vitamin D and inflammatory bowel diseases. Alimentary Pharmacology & Therapeutics. 2014 Jan;39(2):125-36. PMID: 24236989.

99. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. Journal of the American Geriatrics Society. 2011 Dec;59(12):2291-300. PMID: 22188076.

100. Murad MH, Drake MT, Mullan RJ, et al. Clinical review. Comparative effectiveness of drug treatments to prevent fragility fractures: a systematic review and network meta-analysis. Journal of Clinical Endocrinology & Metabolism. 2012 Jun;97(6):1871-80. PMID: 22466336.

101. Murad MH, Elamin KB, Abu Elnour NO, et al. Clinical review: The effect of vitamin D on falls: a systematic review and meta-analysis. Journal of Clinical Endocrinology & Metabolism. 2011 Oct;96(10):2997-3006. PMID: 21795448.

102. Murthy V, Chamberlain RS. Menopausal symptoms in young survivors of breast cancer: a growing problem without an ideal solution. Cancer Control. 2012 Oct;19(4):317-29. PMID: 23037499.

103. Nahas R. Complementary and alternative medicine approaches to blood pressure reduction: An evidence-based review. Canadian Family Physician. 2008 Nov;54(11):1529-33. PMID: 19005120.

104. Nemerovski CW, Dorsch MP, Simpson RU, et al. Vitamin D and cardiovascular disease. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy. 2009 Jun;29(6):691-708. PMID: 19476421.

105. Nicholson I, Dalzell AM, El-Matary W. Vitamin D as a therapy for colitis: a systematic review. Journal of Crohn's & colitis. 2012 May;6(4):405-11. PMID: 22398085.

106. Nnoaham KE, Clarke A. Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. International Journal of Epidemiology. 2008 Feb;37(1):113-9. PMID: 18245055.

107. Nurmatov U, Devereux G, Sheikh A. Nutrients and foods for the primary prevention of asthma and allergy: systematic review and meta-analysis. Journal of Allergy & Clinical Immunology. 2011 Mar;127(3):724-33.e1-30. PMID: 21185068.

108. O'Donnell S, Moher D, Thomas K, et al. Systematic review of the benefits and harms of calcitriol and alfacalcidol for fractures and falls. Journal of Bone & Mineral Metabolism. 2008;26(6):531-42. PMID: 18979152.

109. Peppone LJ, Hebl S, Purnell JQ, et al. The efficacy of calcitriol therapy in the management of bone loss and fractures: a qualitative review. Osteoporosis International. 2010 Jul;21(7):1133-49. PMID: 19960185.

110. Pilz S, Kienreich K, Tomaschitz A, et al. Vitamin d and cancer mortality: systematic review of prospective epidemiological studies. Current Medicinal Chemistry—Anti-Cancer Agents. 2013 Jan 1;13(1):107-17. PMID: 23094928.

111. Pittas AG, Chung M, Trikalinos T, et al. Systematic review: Vitamin D and cardiometabolic outcomes. Annals of Internal Medicine. 2010 Mar 2;152(5):307-14. PMID: 20194237.

112. Poel YHM, Hummel P, Lips P, et al. Vitamin D and gestational diabetes: a systematic review and meta-analysis. European Journal of Internal Medicine. 2012 Jul;23(5):465-9. PMID: 22726378.

113. Pogge E. Vitamin D and Alzheimer's disease: is there a link? Consultant Pharmacist. 2010 Jul;25(7):440-50. PMID: 20601349.

114. Posadzki P, Lee MS, Onakpoya I, et al. Dietary supplements and prostate cancer: a systematic review of double-blind, placebo-controlled randomised clinical trials. Maturitas. 2013 Jun;75(2):125-30. PMID: 23567264.

115. Rabenda V, Bruyere O, Reginster JY. Relationship between bone mineral density changes and risk of fractures among patients receiving calcium with or without vitamin D supplementation: a meta-regression. Osteoporosis International. 2011 Mar;22(3):893-901. PMID: 21060990.

116. Rathi N, Rathi A. Vitamin D and child health in the 21st century. Indian Pediatrics. 2011 Aug;48(8):619-25. PMID: 21918267.

117. Redzic M, Lewis RM, Thomas DT. Relationship between 25-hydoxyvitamin D, muscle strength, and incidence of injury in healthy adults: a systematic review. Nutrition Research. 2013 Apr;33(4):251-8. PMID: 23602241.

118. Reid IR, Bolland MJ, Grey A. Effects of vitamin D supplements on bone mineral density: a systematic review and meta-analysis. Lancet. 2014 Jan 11;383(9912):146-55. PMID: 24119980.

119. Rejnmark L. Effects of vitamin d on muscle function and performance: a review of evidence from randomized controlled trials. Therapeutic Advances in Chronic Disease. 2011 Jan;2(1):25-37. PMID: 23251739.

120. Rejnmark L, Avenell A, Masud T, et al. Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials. Journal of Clinical Endocrinology & Metabolism. 2012 Aug;97(8):2670-81. PMID: 22605432.

121. Renzaho AMN, Halliday JA, Nowson C. Vitamin D, obesity, and obesity-related chronic disease among ethnic minorities: a systematic review. Nutrition. 2011 Sep;27(9):868-79. PMID: 21704500.

122. Richy F, Dukas L, Schacht E. Differential effects of D-hormone analogs and native vitamin D on the risk of falls: a comparative meta-analysis. Calcified Tissue International. 2008 Feb;82(2):102-7. PMID: 18239843.

123. Robien K, Oppeneer SJ, Kelly JA, et al. Drug-vitamin d interactions: a systematic review of the literature. Nutrition in Clinical Practice. 2013 Apr;28(2):194-208. PMID: 23307906.

124. Rojas-Fernandez CH, Maclaughlin EJ, Dore NL, et al. Assessing the potential adverse consequences of supplemental calcium on cardiovascular outcomes: should we change our approach to bone health? Annals of Pharmacotherapy. 2012 May;46(5):696-702. PMID: 22570431.

125. Rush L, McCartney G, Walsh D, et al. Vitamin D and subsequent all-age and premature mortality: a systematic review (Provisional abstract). Database of Abstracts of Reviews of Effects; 2013. p. 679.

126. Schottker B, Ball D, Gellert C, et al. Serum 25-hydroxyvitamin D levels and overall mortality. A systematic review and meta-analysis of prospective cohort studies. Ageing Research Reviews. 2013 Mar;12(2):708-18. PMID: 22343489.

127. Scragg R. Vitamin D and public health: an overview of recent research on common diseases and mortality in adulthood. Public Health Nutrition. 2011 Sep;14(9):1515-32. PMID: 21729467.

128. Seamans KM, Cashman KD. Existing and potentially novel functional markers of vitamin D status: a systematic review. American Journal of Clinical Nutrition. 2009 Jun;89(6):1997S-2008S. PMID: 19403634.

129. Sokol SI, Tsang P, Aggarwal V, et al. Vitamin D status and risk of cardiovascular events: lessons learned via systematic review and meta-analysis. Cardiology in Review. 2011 Jul-Aug;19(4):192-201. PMID: 21646873.

130. Song GG, Bae S-C, Lee YH. Association between vitamin D intake and the risk of rheumatoid arthritis: a meta-analysis. Clinical Rheumatology. 2012 Dec;31(12):1733-9. PMID: 22941259.

131. Sperati F, Vici P, Maugeri-Sacca M, et al. Vitamin d supplementation and breast cancer prevention: a systematic review and meta-analysis of randomized clinical trials. PLoS ONE [Electronic Resource]. 2013;8(7):e69269. PMID: 23894438.

132. Sperati F, Vici P, Maugeri-Sacca M, et al. Vitamin d supplementation and breast cancer prevention: a systematic review and meta-analysis of randomized clinical trials (Provisional abstract). Database of Abstracts of Reviews of Effects; 2013. p. e69269.

133. Stockton KA, Mengersen K, Paratz JD, et al. Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. Osteoporosis International. 2011 Mar;22(3):859-71. PMID: 20924748.

134. Tabesh M, Salehi-Abargouei A, Tabesh M, et al. Maternal vitamin D status and risk of pre-eclampsia: a systematic review and meta-analysis. Journal of Clinical Endocrinology & Metabolism. 2013 Aug;98(8):3165-73. PMID: 23783101.

135. Thiele DK, Senti JL, Anderson CM. Maternal vitamin D supplementation to meet the needs of the breastfed infant: a systematic review. Journal of Human Lactation. 2013 May;29(2):163-70. PMID: 23458952.

136. Thomas GN, Scragg R, Jiang CQ, et al. Hyperglycaemia and vitamin D: a systematic overview. Current Diabetes Reviews. 2012 Jan;8(1):18-31. PMID: 22352447.

137. Thorne-Lyman A, Fawzi WW. Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis. Paediatric and Perinatal Epidemiology. 2012 Jul;26 Suppl 1:75-90. PMID: 22742603.

138. Touvier M, Chan DSM, Lau R, et al. Meta-analyses of vitamin D intake, 25-hydroxyvitamin D status, vitamin D receptor polymorphisms, and colorectal cancer risk. Cancer Epidemiology, Biomarkers & Prevention. 2011 May;20(5):1003-16. PMID: 21378269.

139. Tripkovic L, Lambert H, Hart K, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. American Journal of Clinical Nutrition. 2012 Jun;95(6):1357-64. PMID: 22552031.

140. Urrutia RP, Thorp JM. Vitamin D in pregnancy: current concepts. Current Opinion in Obstetrics & Gynecology. 2012 Mar;24(2):57-64. PMID: 22327734.

141. Uusi-Rasi K, Karkkainen MU, Lamberg-Allardt CJ. Calcium intake in health maintenance—a systematic review. Food & Nutrition Research. 2013;57PMID: 23687486.

142. van der Putten G-J, Vanobbergen J, De Visschere L, et al. Association of some specific nutrient deficiencies with periodontal disease in elderly people: A systematic literature review. Nutrition. 2009 Jul-Aug;25(7-8):717-22. PMID: 19539173.

143. van der Rhee H, Coebergh JW, de Vries E. Sunlight, vitamin D and the prevention of cancer: a systematic review of epidemiological studies. European Journal of Cancer Prevention. 2009 Nov;18(6):458-75. PMID: 19730382.

144. van der Rhee H, Coebergh JW, de Vries E. Is prevention of cancer by sun exposure more than just the effect of vitamin D? A systematic review of epidemiological studies. European Journal of Cancer. 2013 Apr;49(6):1422-36. PMID: 23237739.

145. van der Schaft J, Koek HL, Dijkstra E, et al. The association between vitamin D and cognition: A systematic review. Ageing Research Reviews. 2013 Sep;12(4):1013-23. PMID: 23727408.

146. van Holten TC, Waanders LF, de Groot PG, et al. Circulating biomarkers for predicting cardiovascular disease risk; a systematic review and comprehensive overview of meta-analyses. PLoS ONE [Electronic Resource]. 2013;8(4):e62080. PMID: 23630624.

147. Verheyden GS, Weerdesteyn V, Pickering RM, et al. Interventions for preventing falls in people after stroke. Cochrane Database of Systematic Reviews. 2013;5:CD008728. PMID: 23728680.

148. Villar LM, Del Campo JA, Ranchal I, et al. Association between vitamin D and hepatitis C virus infection: a meta-analysis. World Journal of Gastroenterology. 2013 Sep 21;19(35):5917-24. PMID: 24124339.

149. Wang D, Velez de-la-Paz OI, Zhai JX, et al. Serum 25-hydroxyvitamin D and breast cancer risk: a meta-analysis of prospective studies (Provisional abstract). Database of Abstracts of Reviews of Effects; 2013. p. epub.

150. Wang D, Velez de-la-Paz OI, Zhai JX, et al. Serum 25-hydroxyvitamin D and breast cancer risk: a meta-analysis of prospective studies. Tumour Biology. 2013 Dec;34(6):3509-17. PMID: 23807676.

151. Wang H, Xia N, Yang Y, et al. Influence of vitamin D supplementation on plasma lipid profiles: a meta-analysis of randomized controlled trials. Lipids in Health & Disease. 2012;11:42. PMID: 22433171.

152. Wang L, Manson JE, Song Y, et al. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. Annals of Internal Medicine. 2010 Mar 2;152(5):315-23. PMID: 20194238.

153. Wei MY, Garland CF, Gorham ED, et al. Vitamin D and prevention of colorectal adenoma: a meta-analysis. Cancer Epidemiology, Biomarkers & Prevention. 2008 Nov;17(11):2958-69. PMID: 18990737.

154. Wheless L, Black J, Alberg AJ. Nonmelanoma skin cancer and the risk of second primary cancers: a systematic review. Cancer Epidemiology, Biomarkers & Prevention. 2010 Jul;19(7):1686-95. PMID: 20570907.

155. Winzenberg T, Powell S, Shaw KA, et al. Effects of vitamin D supplementation on bone density in healthy children: systematic review and meta-analysis. BMJ. 2011;342:c7254. PMID: 21266418.

156. Winzenberg TM, Powell S, Shaw KA, et al. Vitamin D supplementation for improving bone mineral density in children. Cochrane Database of Systematic Reviews. 2010(10):CD006944. PMID: 20927753.

157. Witham MD, Nadir MA, Struthers AD. Effect of vitamin D on blood pressure: a systematic review and meta-analysis. Journal of Hypertension. 2009 Oct;27(10):1948-54. PMID: 19587609.

158. Wolpin BM, Ng K, Bao Y, et al. Plasma 25-hydroxyvitamin D and risk of pancreatic cancer. Cancer Epidemiology, Biomarkers & Prevention. 2012 Jan;21(1):82-91. PMID: 22086883.

159. Wu SH, Ho SC, Zhong L. Effects of vitamin D supplementation on blood pressure. Southern Medical Journal. 2010 Aug;103(8):729-37. PMID: 20622727.

160. Yamshchikov AV, Desai NS, Blumberg HM, et al. Vitamin D for treatment and prevention of infectious diseases: a systematic review of randomized controlled trials. Endocrine Practice. 2009 Jul-Aug;15(5):438-49. PMID: 19491064.

161. Yin L, Grandi N, Raum E, et al. Meta-analysis: longitudinal studies of serum vitamin D and colorectal cancer risk. Alimentary Pharmacology & Therapeutics. 2009 Jul 1;30(2):113-25. PMID: 19392870.

162. Yin L, Grandi N, Raum E, et al. Meta-analysis: serum vitamin D and breast cancer risk. European Journal of Cancer. 2010 Aug;46(12):2196-205. PMID: 20456946.

163. Yin L, Grandi N, Raum E, et al. Meta-analysis: Circulating vitamin D and ovarian cancer risk. Gynecologic Oncology. 2011 May 1;121(2):369-75. PMID: 21324518.

164. Yin L, Ordonez-Mena JM, Chen T, et al. Circulating 25-hydroxyvitamin D serum concentration and total cancer incidence and mortality: A systematic review and meta-analysis. Preventive Medicine. 2013 Dec;57(6):753-64. PMID: 24036014.

165. Yin L, Raum E, Haug U, et al. Meta-analysis of longitudinal studies: Serum vitamin D and prostate cancer risk. Cancer Epidemiology. 2009 Dec;33(6):435-45. PMID: 19939760.

166. Zheng Y, Zhu J, Zhou M, et al. Meta-analysis of long-term vitamin d supplementation on overall mortality. PLoS ONE [Electronic Resource]. 2013;8(12):e82109. PMID: 24349197.

167. Zipitis CS, Akobeng AK. Vitamin D supplementation in early childhood and risk of type 1 diabetes: a systematic review and meta-analysis. Archives of Disease in Childhood. 2008 Jun;93(6):512-7. PMID: 18339654.

168. Zittermann A, Gummert JF, Borgermann J. The role of vitamin D in dyslipidemia and cardiovascular disease. Current Pharmaceutical Design. 2011;17(9):933-42. PMID: 21418036.

169. Zittermann A, Iodice S, Pilz S, et al. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. American Journal of Clinical Nutrition. 2012 Jan;95(1):91-100. PMID: 22170374.

Background Articles—N=10

1. Drugs for postmenopausal osteoporosis. Treatment Guidelines From the Medical Letter. 2008 Oct;6(74):67-74; quiz 5-6. PMID: 18800025.

2. Bolland MJ, Grey A, Gamble GD, et al. Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. American Journal of Clinical Nutrition. 2011 Oct;94(4):1144-9. PMID: 21880848.

3. Grant WB. Effect of interval between serum draw and follow-up period on relative risk of cancer incidence with respect to 25-hydroxyvitamin D level: Implications for meta-analyses and setting vitamin D guidelines. Dermato-endocrinology. 2011 Jul;3(3):199-204. PMID: 22110780.

4. Grant WB. Effect of follow-up time on the relation between prediagnostic serum 25-hydroxyvitamin D and all-cause mortality rate. Dermato-endocrinology. 2012 Apr 1;4(2):198-202. PMID: 22928077.

5. Hofmann JN, Yu K, Horst RL, et al. Long-term variation in serum 25-hydroxyvitamin D concentration among participants in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Cancer Epidemiology, Biomarkers & Prevention. 2010 Apr;19(4):927-31. PMID: 20332255.

6. Niramitmahapanya S, Harris SS, Dawson-Hughes B. Type of dietary fat is associated with the 25-hydroxyvitamin D3 increment in response to vitamin D supplementation. Journal of Clinical Endocrinology & Metabolism. 2011 Oct;96(10):3170-4. PMID: 21816779.

7. O'Connor E, Molgaard C, Michaelsen KF, et al. Vitamin D-vitamin K interaction: effect of vitamin D supplementation on serum percentage undercarboxylated osteocalcin, a sensitive measure of vitamin K status, in Danish girls. British Journal of Nutrition. 2010 Oct;104(8):1091-5. PMID: 20487587.

8. Ross AC, Manson JE, Abrams SA, et al. The 2011 Dietary Reference Intakes for Calcium and Vitamin D: what dietetics practitioners need to know. Journal of the American Dietetic Association. 2011 Apr;111(4):524-7. PMID: 21443983.

9. Vanstone MB, Oberfield SE, Shader L, et al. Hypercalcemia in children receiving pharmacologic doses of vitamin D. Pediatrics. 2012 Apr;129(4):e1060-3. PMID: 22412034.

10. Wallace RB, Wactawski-Wende J, O'Sullivan MJ, et al. Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. American Journal of Clinical Nutrition. 2011 Jul;94(1):270-7. PMID: 21525191.

Appendix G. Serum Vitamin D Assay Reporting in Randomized Controlled Trials (RCTs)

Author, Year	Species	Method	Location of Study/Year of Assay	Inter-/Intra-Assay Variability	Reference Standard[a]
Studies in Original Report					
Bjorkman, 2008[263]	Serum 25(OH)D	HPLC[307]	Finland/ assay dates not reported	Limit of quantification: 10 nmol/L. Intra-assay coefficient of variation: 5.6% (21.6 nmol/l; n=14) and 3.7% at 138nmol/l (n=15). Total CV: 7.3% at 16.4nmol/l (n=12) and 5.7% at 167nmol/l(n=15)	Not Reported (NR)
Blum, 2008[279]	Serum 25(OH)D	Competitive protein binding assay	US/assay dates not reported	NR	NR
Bolton-Smith, 2007[274]	Serum 25(OH)D	Radioimmunoassay (RIA) (DiaSorin, Wokingham, UK)	UK/assay dates not reported	NR	NR
Bunout, 2006[183]	Serum 25(OH)D	Not described	NR	NR	NR
Chan, 1982[300]	Serum 25(OH)D	Competitive protein binding assay[308]	US/assay dates not reported	Coefficient of variation: 9%	NR
Chapuy, 1997[280]	Serum 25(OH)D	RIA (Incstar Corp, Stillwater, MN)	France/assay dates not reported	Intra-assay variance: 5% Inter-assay variance: 11%	NR
Chel, 2008[281]	Serum 25(OH)D	RIA (DiaSorin, Stillwater MN)	Netherlands/assay dates not reported	Inter-assay coefficient of variation:10% at 30 nmol/L	NR
Dawson-Hughes, 1997[289]	Plasma 25(OH)D Plasma (1,25)D2	25(OH)D: Competitive protein binding assay[309] 1,25 di(OH)D: Competitive protein-binding method[310]	US/assay dates not reported	NR	NR
DeRoisy, 2002[282]	Serum 25(OH)D	RIA (Incstar, Stillwater, MN, USA).	Belgium/assay dates not reported	Intra-assay coefficient of variation: 8% Inter-assay coefficient of variation: < 12%	NR

Author, Year	Species	Method	Location of Study/Year of Assay	Inter-/Intra-Assay Variability	Reference Standard[a]
El-Hajj-Fuleihan, 2006[48]	Serum 25(OH)D Serum 1,25-dihydroxyvitamin D (1,25(OH)2D)	25(OH)D: competitive protein binding assay (DiaSorin, Incstar, Saluggia, Italy) 1,25(OH)2D): RIA (IDS Immuno-Diagnostic Systems, Boldon, UK).	NR	Intra- and interassay Coefficients of Variation <13% at a serum concentration of 47 ng/ml. Intra- and interassay coefficients of variation < 10% at serum concentrations between 10 and 100 pg/ml	NR
Harris, 2002[290]	Plasma 25(OH) D3 Plasma 25(OH)D	25(OH)D3: high performance liquid chromatography 25(OH)D: competitive protein binding assay	US/Assay dates not reported	NR	NR
Heaney, 2003[291]	Serum 25(OH)D	RIA (Nichols Institute Diagnostics, San Juan Capistrano CA)	US/assay dates not reported	NR	NR
Heikkinen, 1998[292]	Serum 25OHD and 1,25(OH)2D	25OHD and 1,25(OH)2D : competitive protein binding assays using vitamin D binding proteins following purification on dual HPLC with UV detection[311]	Finland/assay dates not reported but conducted at baseline and 1 year later	Interassay coefficient of variation (CV) was less than 8% in serum 25OHD analysis	NR
Himmelstein, 1990[283]	Serum 1,25(OH)2D 25OHD	1,25(OH)2D: calf thymus radioreceptor assay[310] 25(OH)D: competitive protein binding assay[309]	US/assay dates not reported	1,25(OH)2D Intra-assay coefficient of variation:5% Inter-assay coefficient of variation: 11% 25(OH)D: Intra-assay coefficient of variation:5% Inter-assay coefficient of variation: 10%	NR
Honkanen, 1990[293]	Serum 25(OH)D	25(OH)D: competitive protein binding assay[311]	Finland/assay dates not reported	NR	NR
Jensen, 2002[294]	Serum 25(OH)D	Competitive protein-binding assay (Nichols Institute Diagnostics, San Juan Capistrano, CA)	US/assay dates not reported	NR	NR
Kenny, 2003[284]	Serum 25(OH)D	Competitive protein binding assay (Endocrine Sciences Inc., Calabasas Hills, CA)	US/assay dates not reported	Intra-assay coefficient of variation: <10%	NR

Author, Year	Species	Method	Location of Study/Year of Assay	Inter-/Intra-Assay Variability	Reference Standard[a]
Krieg, 1999[285]	Serum 25(OH)D	Protein binding assay (Amersham Life Science, Little Chalfont, Bucks, UK)	Switzerland/assay dates not reported	NR	NR
Nelson, 2009[295]	Serum 25(OH)D	RIA	US/2005–2006	Intra-assay and inter-assay coefficients of variation <10%	NR
Orwoll, 1988[296]	Serum 25(OH)D 1,25(OH)2D 24,25(OH)2D	25(OH)D: Competitive protein binding assay[312,313] 1,25(OH)2D and 24,25(OH)2D determined by Anthony Norman[314]	US/assay dates not reported	NR	NR
Patel, 2001[297]	Serum 25(OH)D	RIA (INCSTAR)	UK/assay dates not reported	Sensitivity: 7.5nmol/l Intra-assay precision: 6.1% Inter-assay precision: 15.6%	NR
Pfeiffer, 2001[238]	Serum 25OHD3, and 1,25-(OH)2D3	RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA)	Germany/assay dates not reported	Coefficients of variation: 5.5–7.9%	NR
Pfeiffer, 2000[286]	Serum 25OHD3, and 1,25-(OH)2D3	RIA (Nichols Institute Diagnostics, San Juan Capistrano, CA)	Germany/assay dates not reported	Coefficients of variation: 5.5–7.9%	NR
Riis, 1984[298]	Serum 25OHD3, 24, 25 $(OH)_2D3$, and 1,25-$(OH)_2D3$	25(OH)D: UV detection 1,25(OH)2D and 24,25(OH)2D determined by competitive protein binding assay[315]	Denmark/assay dates not reported	Intra-assay and inter-assay coefficients of variation: 1,25(OH)2D: 13% and 15% 24, 25(OH)2D: 14% and 17% 25(OH)D: 10% and 12%	NR
Trang, 1998[299]	Serum 25(OH)D 1,25(OH)2D	25(OH)D: RIA (INCSTAR, Stillwater MN) 1,25(OH)2D: calf thymus competitive protein binding assay	Canada/assay dates not reported	25(OH) D consistently within 1SD of the method group mean for the International External Quality Assessment Scheme	Results of the 25(OH)D assay method were consistently within 1 SD of the method group mean in the International External Quality Assessment Scheme proficiency survey for this metabolite
Sorva, 1991[287]	Serum 25(OH)D and 1,25-(OH)2D3	25(OH)D: competitive protein binding assay[316] 1,25(OH)2D3: competitive protein binding assay[310]	Finland/assay dates not reported	NR	NR
Zhu, 2008[275]	Serum 25(OH)D	RIA (DiaSorin, Stillwater MN)	Australia/assay dates not reported	NR	NR

Author, Year	Species	Method	Location of Study/Year of Assay	Inter-/Intra-Assay Variability	Reference Standard[a]
Studies Identified for Current Report					
Gaanmaa, 2012[278]	Plasma 25(OH)D	CLIA TOTAL (LIAISON DiaSorin, Stillwater, MI, USA	US/4/10–6/10	NR	NR
Gepner, 2012[229]	Serum 25(OH)D	HPLC[317,318]	US/assay dates not reported	NR	NR
Islam, 2010[267]	Serum (OH)D	RIA OCTEIA (IDS, Boldon, UK)	Finland/assay dates not reported	Intra-and inter-assay coefficients of variation: 5·4 and 7·0 %	DEQAS
Jorde, 2010[230]	Total 25(OH)D	RIA (DiaSorin, Stillwater MN)	Norway / Assay dates not reported	Intra-assay and total coefficient of variation: 6% and 14%	NR
Karkainnen, 2010[269]	Serum 25(OH)D	RIA (DiaSorin, Stillwater MN)	Finland/assay dates not reported	Coefficient of Variation: 8.2% to 11.0%	NR
Kukuljian, 2011[272]	Serum 25(OH)D	RIA kit DiaSorin (Stillwater, MN, USA)	Australia/assay dates not reported	Coefficient of Variation: 3.9 – 5.8%	NR
Li-Ng, 2009[150]	Serum 25(OH)D	RIA kit DiaSorin (Stillwater, MN, USA)	US/assay dates not reported	Intra-assay Variability: 4.1% Inter-assay Variability:7.0%.	DEQAS
MacDonald, 2013[245]	Serum 25(OH)D2 and 3	HPLC-tandem mass spectrometry	UK/assay dates not reported	Interassay coefficients of variation <10%	NIST standard used. Lab also participates in DEQAS
Molgaard, 2010[248]	Serum 25(OH)D	HPLC-based assay[319]	Denmark/assay dates not reported	Intra- and inter-assay coefficients of variability: 4.3% and 6.3%, respectively	DEQAS
Nieves, 2012[244]	Serum 25(OH)D and 1,25di(OH)D	RIA kit DiaSorin (Stillwater, MN, USA)	US/assay dates not reported	Coefficient of variation<12%	NR
Pfeifer, 2009[186]	Serum 25(OH)D	RIA (Immunodiagnostic Systems, Boldon, UK)	Germany/assay dates not reported	NR	NR (validated against HPLC)
Salehpour, 2012 [234]	Serum 25(OH)D	Enzyme immunoassay (Immunodiagnostic Systems Limited).	Iran/assay dates not reported	Intra- and inter-assay coefficients of variation: 6·9 and 8·1 %, respectively	NR
Salovaara, 2010[260]	Serum 25(OH)D	RIA kit DiaSorin (Stillwater, MN, USA)	Finland/assay dates not reported	Coefficient of variation: 8.2% to 11.0%	NR
Toxqui, 2013[228]	Serum 25(OH)D	Enzyme immunoassay (Immunodiagnostic Systems Limited, UK).	Spain/assay dates not reported	Intra- and inter-assay coefficients of variation: 5.6%, 6.4%, respectively	NR
Wamberg, 2013[236]	Serum 25(OH)D2 and 3	HPLC tandem mass spec[320]	Denmark/assay dates not reported	NR	NR
Witham, 2013[235]	Serum 25(OH)D	Enzyme immunoassay (Immunodiagnostic Systems Limited, UK).	UK/assay dates not reported	NR	NR
Wood, 2012[231]	Serum 25(OH)D2 and 3	HPLC tandem mass spec	UK/assay dates not reported	Coefficients of variation<10%	NR

Author, Year	Species	Method	Location of Study/Year of Assay	Inter-/Intra-Assay Variability	Reference Standard[a]
Zhu, 2010[188]	Serum 25OH)D	RIA kit DiaSorin (Stillwater, MN, USA)	Australia/assay dates not reported	NR	NR

Legend:
[a]The reference standard refers to a sample whose concentration of 25(OH)D has been ascertained by a recognized entity, such as the United States National Institute of Standards and Technology (NIST), that is used to establish the reliability of an assay.
CLIA=chemiluminescence immunoassay CV=Coefficient of Variation; 25(OH)D=25-hydroxyvitamin D; 1,25$(OH)_2$D=1,25-Dihydroxyvitamin D; 1,25 di(OH)D=1,25-dihydroxyvitamin D; 24,25$(OH)_2$=Dihydroxyvitamin D; HPLC= High Performance Liquid Chromatography; nmol=nanomoles; NR=Not Reported; RCT=Randomized Controlled Trial(s); RIA=radioimmunoassay; UV=Ultraviolet

Appendix H. Studies Reporting Key Outcomes Stratified by Vitamin D Assay Method

Tables 4, 5: Growth (vitamin D)
Tables 6, 7: Birth weight (vitamin D)
Tables 14–17: Total cancer/cancer mortality (vitamin D)
Tables 18, 19: Prostate cancer (vitamin D)
Tables 26, 27: Breast cancer (vitamin D)
Tables 28, 29: Pancreatic cancer (vitamin D)
Tables 30c and d, 31c and d: Infectious illnesses (vitamin D)
Tables 32a, 33a: Preeclampsia (vitamin D)
Tables 35d, 36d: Fracture (vitamin D)
Tables 38, 39: All-cause mortality (vitamin D)
Tables 42, 43: Blood pressure (vitamin D)
Tables 44, 45: Bone mineral density (vitamin D)
Tables 65, 66: Bone mineral density (vitamin D+calcium)

List of Acronyms and Abbreviations Included in Tables

Abbreviation	Term	Abbreviation	Term
ACS	Aortic calcification score	MONICA	Multinational MONItoring of trends and determinants in CArdiovascular disease Study
ADL	Activities of Daily Living	MI	Myocardial infarction
ASA	Acetyl salicylic acid (aspirin)	n	Number
ATBC	Alpha Tocopherol, Beta Carotene Cancer Prevention Study	na	Not applicable
BMC	Bone mineral content	nd	No data
BMD	Bone mineral density	NHS	Nurses Health Study
BMI	Body mass index	nr	Not reported
BP	Blood pressure	NSAIDS	Non-steroidal Antiinflammatories
Ca	Calcium	NHANES	National Health and Nutrition Examination Survey
CHS	Cardiovascular Health Study		
CKD	Chronic kidney disease	nmol	nanomoles
CPS	Cancer Prevention Study		
CRC	Colorectal cancer	OR	Odds ratio
CRP	C-reactive protein		
CVD	Cardiovascular disease	PASE	Physical Activity Score For The Elderly
d	Day	PLCO	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
DBP	Diastolic blood pressure	PTH	Parathyroid hormone
DM	Diabetes mellitus	Q	Quartile
Dx	Diagnosis	RCT	Randomized controlled trial
eGFR	Estimated glomerular filtration rate	RIA	radioimmunoassay;
EPIC	European Prospective Investigation into Cancer and Nutrition	RR	Relative risk
ESTHER	EStrogen and THromboEmbolism Risk Study	SC	Size-corrected
GFR	Glomerular filtration rate	SD	Standard deviation
HDL	High-density lipoprotein	SBP	Systolic blood pressure
HLA	Human leukocyte antigen		
HPFS	Health Professionals Follow-Up Study	SES	Socioeconomic status
HPLC	high performance liquid chromatography	SPPB	Secondary-Short Physical Performance Battery
HR	Hazard ratio	TUAG	Timed Up and Go
HTN	Hypertension	UK	United Kingdom
InChianti	Invecchiare nel Chianti	UV	Ultraviolet
INTAPP	International Trial of Antioxidants in the Prevention of Pre-eclampsia	Vit	Vitamin
IQR	Interquartile range	VTE	Venous thromboembolism
IU	International Units	WHI	Women's Health Iniative
KORA	Cooperative Health Research in the Region Augsburg	Wk	Week
LDL	Low-density lipoprotein	Y, y	year
MEC	Mobile Examination Center	YRS	Years
MESA	Multi-ethnic Study of Atherosclerosis		
MI	Myocardial infarction		

Table 4. Vitamin D and growth outcomes: Characteristics of interventional studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Radioreceptor assay						
Maxwell 1981[51] Brooke 1980[47] UK (51ºN) [6793058] [6989438]	• Health status • Mean age (range/SD), y • Male (%)	pregnancy nd 0	25(OH)D at 28-32 wk: 20.1 nmol/L	Vit D 1000 IU/d 3rd trimester only	nd	First generation Asian immigrants only
El-Hajj 2006[48] Lebanon (33ºN) [16278262]	• Health status • Mean age (range/SD), y • Male (%)	healthy 13.2 (10–17) 0	25(OH)D 35 nmol/L; dietary Ca 677 mg/d	Vit D_3 200 IU/d vs. 2000 IU/d vs. placebo x 1 y	98% in placebo; 98% in low dose; 97% in high dose	7.4 h sun exposure/wk
Mallet 1986[53] France (48º N) [3755517]	• Health status • Mean age (range/SD), y • Male (%)	pregnancy newborn nd	Ca intake 550 to 1000 mg/d in 55% of the subjects	Vit D 1000 IU/d vs. 200,000 IU 1x dose	nd	
Radioimmunoassay						
Wagner 2006[52] Charleston, US (32ºN) [17661565]	• Health status • Mean age (range/SD), y • Male (%)	Fully lactating; <1 mo postpartum 29 0	Lactating mother's dietary Vit D 273 IU/d; dietary calcium intake: 1125 mg/d;	Mother Vit D_3 400 IU/d + infant 300 IU/d vs. mother 6400 IU/d + infant 0 IU/d	≥80% in mothers; as low as 61% for infants	78% white; 11% black; 11% Hispanic
Hollis, 2011[1] Charleston, US	• Health status • Mean age (range/SD), y • Male (%)	Healthy 27 (18–41/5.6) 0%	serum: delivered group- 59.5 23.8 nmol/L (6.0–172.5) exited group- 50.5 25.1nmol/L (6.5–120.5) vit D intake: 400 IU group- 181.6 +/- 108.4 IU/d, 2000 IU group- 195.8 +/- 135.0, 4000 IU group- 204.2 +/-148.2 calcium intake: 400 IU group-1063.6 +/-539.6 mg/d, 2000 IU group- 993.9 +/-514.0 mg/d, 4000 IU group- 1073.6+/- 491.9 mg/d	Birth weight: Vit D 4000 IU vs. Vit D 2000 IU vs. Vit D 400 IU	69% (400-IU group), 68% (2000-IU group), and 69% (4000-IU group, p¼0.9)	**Assignment to the interventions was only partially random: Baseline serum 25(OH)D also partly determined assignment**

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Kalra, 2012[43] India	• Health status • Mean age (range/SD), y • Male (%)	nd 26.7 (SD 4.0) 0%	Table 2: Group 1–31.7 nmol/L (14.0–57.2) Group 2- 32.0 nmol/L (14.5–45.7)	Birth weight: 3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation) vs. 1500 mg cholecalciferol (one dose 2nd trimester) Length at Birth: 3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation) vs. 1500 mg cholecalciferol (one dose 2nd trimester)	nd	age= Group 1 from table 2
Roth 2013[44] Bangladesh	• Health status • Mean age (range/SD), y • Male (%)	Healthy 22.4 (SD 3.5) 0%	Serum 25(OH)D placebo: 44.0 ± 20.9 nmol/l vitamin D: 45.4 ± 18.4 nmol/l	Birth weight: 35000 IU Vit D3 3rd trimester vs. Placebo Length at birth: 35000 IU Vit D3 3rd trimester vs. Placebo	99.2 ± 2.7%	
Wagner 2013[42] US	• Health status • Mean age (range/SD), y • Male (%)	nd 27 (18–41) 0%	61.5 nmol/L	2000 IU vit D3 vs. 4000 IU vit D3 vs. control	NR	

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Assay method not reported						
Marya 1981[54] India (28ºN) [7239350]	• Health status	no pregnancy-related complications	Expectant mother's daily milk intake <500 mL; dietary Vit D <30 IU/d	Vit D 1200 IU/d + Ca 375 mg/d (3rd trimester) or Vit D 1.2 mil IU (total; 600,000 IU in 7th & 8th mo) or no supplement	nd	
Marya 1988[50] India (28ºN) [3243609]	• Health status • Mean age (range/SD), y • Male (%)	no pregnancy-related complications 24 0	Expectant mother's dietary Vit D 35 IU/d; calcium 429 mg/d	Mother Vit D 1.2 mil IU (total; 600,000 IU vit D_2 in 7th & 8th mo) vs. no supplement	nd	
Feliciano 1994[49] China (22ºN to 47ºN) [8078115]	• Health status • Mean age (range/SD), y • Male (%)	healthy term newborn nd	86% infant breastfed until 5–6 mo	Vit D 100 IU/d vs. 200 IU/d vs. 400 IU/d	nd	

Table 5. Vitamin D and growth outcomes: Characteristics of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Radioimmunoassay												
Morley 2006[56] Australia (38ºS) [16352684]	• Health status	singleton pregnancy; no disease	• Assay method	RIA	Length and weight in offspring stratified by mother's 25(OH)D		X	X		X	X	99% white; excluded dark skin or women with concealing clothing
	• Mean age (range/SD), y	29										
	• Male (%)	0	• Season blood drawn	winter & summer								
Gale 2008[55] PAHSG UK (50ºN) [17311057]	• Health status	singleton pregnancy <17 wk	• Assay method	RIA	Length and weight in offspring stratified by mother's 25(OH)D		X			X		White only
	• Mean age (range/SD), y	26.3										
	• Male (%)	0	• Season blood drawn	nd								
Radioimmunoassay and chemiluminescence assay averaged together												
Burris 2012 [45] Massachusetts, US	• Health status	nd			Weight in offspring stratified by mother's 25(OH)D		X	X		X		
	• Mean age (range/SD), y	33 (SD 4.5)										
	• Male (%)	0%										
HPLC and tandem mass spectrometry												
Gernand, 2013[46] US	• Health status	Singleton gestation			Weight in offspring stratified by mother's 25(OH)D		X	X		X	X	
	• Mean age (range/SD), y	nd										
	• Male (%)	0%										

Table 6. Vitamin D and growth outcomes: Results of RCTs (updated from original report)

Author Year Study Name[PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change (SD)	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Radioreceptor assay														
Maxwell 1981[51] Brooke 1980[47] [6793058] [6989438]	Pregnant women & infant 0–6 mo (Asians)	Infant birth weight	2°	until delivery	Vit D 1000 IU	59	g	NA	Final 3157	3037, 3277	Diff 123	-50, 296[C]	NS	B
					Control	67		NA	3034	2909, 3159				
		Infant birth length	2°	until delivery	Vit D 1000 IU	59	cm	NA	Final 49.7	49.6, 49.8	Diff 0.2	0.1, 0.3[C]	NS	
					Control	67		NA	49.5	49.4, 49.6				
El-Hajj 2006[48] [16278262]	9–18 y female, premenarche	Height	2°	1 y	Vit D_3 2000 IU	nd, ≤34 total	%	nd	5.60%	~4.8, 6.4[C]	~1.8%	~0.6, 3.0[C]	0.07	C
					Vit D_3 200 IU			nd	5.00%	~4.2, 5.8[C]	~1.2%	~-0.01, 2.4[C]		
					Placebo			nd	3.80%	~0.9, 6.7[C]				
		Weight	2°	1 y	Vit D_3 2000 IU	nd, ≤34 total	%	nd	18.40%	~14.7, 22.1[C]	~3.5%	~-1.3, 8.3[C]	0.25	
					Vit D_3 200 IU			nd	15.30%	~12.5, 18.1[C]	~0.4	-3.7, 4.5[C]		
					Placebo			nd	14.90%	~11.8, 18.0[C]				
Mallet 1986[53] France (48º N) [3755517]	Pregnant women & infant 0–6 mo	Birth weight	2°	delivery	Vit D 1000 IU	21[D]	g	NA	Final 3370 (80)		Diff 160		NS	C
					Vit D 200,000 IU 1x dose	27[D]		NA	3210 (90)					
Radioimmunoassay														
Wagner 2006[52] [17661565]	Lactating mothers & infant 0–6 mo; 7 mo–2 y	Infant weight[B]	1°	7 mo	Mother (400) +infant (300)	10	g	NA	Final 7600	7100, 8100	Diff -800	-2300, 700[C]	0.3	C
					Mother (6400) +infant (0)	9		NA	8400	7700, 9100				
		Infant length	1°	7 mo	Mother (400) +infant (300)	10	cm	NA	Final 65.5	64.4, 66.6	Diff -3.8	-7.8, 0.2[C]	0.06	
					Mother (6400)	9		NA	69.3	67.4,				

Author Year Study Name[PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change (SD)	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
					+infant (0)					71.2				
Hollis 2011[1]	Pregnant or lactating women	Birth weight	2°	Delivery	Vit D 4000 IU	117	g	NR	Final 3284.6	3175.2, 3394.0	+62.8	-103.4, 229.0	0.23	A
					Vit D 2000 IU	122			Final 3360.1	3255.2, 3465.0	+138.3	-24.4, 301.0		
					Vit D 400 IU	111			Final 3221.8	3094.9, 3348.8				
Kalra 2012[43]	Pregnant or lactating women between 12–24 weeks gestation	Birth weight	1°	Delivery	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)	35	kg	NR	Final 3.03	1.71, 4.35	-0.05	-1.92, 1.82	0.96	C
					1500 mg cholecalciferol (one dose 2nd trimester)	36	kg		Final 3.08	1.71, 4.45				
		Length at birth	1°	Delivery	3000 mg cholecalciferol (one dose 2nd trimester and 28 weeks gestation)	35	cm	NR	Final 50.1	49.8, 50.4	-0.2	-0.6, 0.2	0.35	
					1500 mg cholecalciferol (one dose 2nd trimester)	36	cm		Final 50.3	50.0, 50.6				
Roth 2013[44]		Birth weight	2°	Delivery	35000 IU Vit D^3 3rd trimester	73	g	NR	Final 2802	2675, 2929	+14	-138, 166	0.86	A
					Placebo	74	g		Final 2788	2700, 2876				
		Length at birth	2°	Delivery	35000 IU Vit D^3 3rd trimester	73	cm	NR	Final 48.2	47.6, 48.8	+0.2	-0.5, 0.9	0.55	
					Placebo	74	cm		Final 48	47.5, 48.5				
Wagner 2013[42]		neonatal birth weight	1°		2000 IU vit D^3	201	g	NR	Final 3382	sd=759	+149	-21, 319	0.09	B
					4000 IU vit D^3	193			Final 3231	sd=632	-2	-154, 150	0.98	
					control	110			Final 3233	sd=668				

Author Year Study Name[PMID]	Life Stage	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change (SD)	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Assay method not reported														
Marya 1981[54] [7239350][E]	Pregnant women & infant 0–6 mo	Birth weight	2º	Delivery	Vit D 1.2 mil IU total	20	g	NA	Final 3140	2940, 3340	Diff 410	166, 654[C]	0.001	C
					Vit D 1200 IU + 375 mg Ca (3rd trimester)	25	g	NA	Final 2890	2760, 3020	Diff 160	0, 320[C]	0.05	
					No supplement	75		NA	2730	2650, 2810				
Marya 1988[50] India [3243609]	Pregnant women & infant 0–6 mo	Birth weight	1º	Delivery	Vit D 1.2 mil IU total	100	g	NA	Final 2990	2920, 3060	Diff 190	90, 290[C]	<0.001	C
					No supplement	100		NA	2800	2730, 2870				
		Birth length	2º		Vit D 1.2 mil IU total	100	cm	NA	Final 50.06	49.7, 50.4	Diff 1.6	1.1, 2.1[C]	<0.001	
					No supplement	100		NA	48.45	48.1, 48.8				
Feliciano 1994[49] [8078115]	0–6 mo	Weight gain born in spring, N. China[A]	1°	6 mo	Vit D 400 IU	12	g	nd	3745	2613, 4877	-463	-1852, 926[C]	NS	C
					Vit D 200 IU	13		nd	5296	4718, 5874	1088	96, 2080[C]	NS	
					Vit D 100 IU	17		nd	4208	3402, 5013				
		Length gain born in spring, N. China	1°	6 mo	Vit D 400 IU	12	cm	nd	18.8	17.4, 20.2	-0.5	-2.7, 1.7[C]	NS	
					Vit D 200 IU	13		nd	19	18.1, 19.9	-0.3	-2.2, 1.6[C]	NS	
					Vit D 100 IU	15		nd	19.3	17.6, 21.0				

[A]See Table 1 in original paper for complete results stratified by North vs. South China and birth in spring vs. fall

[B]See Table 3 in original paper for results on 1 mo and 4 mo

[C]Estimated from available data

[D]Estimated from number of mothers; number of infants not reported

[E]This is not an RCT; the supplemented groups were randomized, but not the control (non-supplemented group); data from comparisons between the supplemented groups not reported.

Table 7. Vitamin D and growth outcomes: Results of cohort studies (updated from original report)

Author Year Study Name PMID	Life Stage	Outcome (n/N; Incidence)	Followup Duration	Maternal 25(OH)D concentration, nmol/L	No. in Category	Final value	Final SD	P value	Study Quality
Radioimmunoassay									
Morley 2006[56] Australia [16352684]	Pregnant women; infant 0–6 mo	Birth weight (N=374)	Delivery	<28 at 28-32 wk	27	3397 g	57	NS	B
				≥28 at 28–32 wk	347	3555	52		
		Birth length (N=374)	Delivery	<28 at 28–32 wk	27	49.8 cm	2.7	NS	
				≥28 at 28–32 wk	347	50.4	2.4		
Gale 2008[55] PAHSG, UK [17311057]	Pregnant women; infant 0–6 mo	Birth weight (N=466)	Delivery	<30 (Quartile)	nd	3.38 kg	0.46	0.25[A]	C
				30–50	nd	3.4	0.56		
				50–75	nd	3.49	1.57		
				>75	nd	3.43	0.51		
		Weight at 9 mo (N=440)	9 mo	<30	nd	15.9	1.14	0.58	
				30–150	nd	15.8	1.26		
				50–175	nd	16.1	1.34		
				>75	nd	15.9	1.09		
		Weight at 9 y (N=178)	9 y	<30	nd	27.4 kg	1.19	0.1	
				30–150	nd	29.4	1.21		
				50–175	nd	30	1.2		
				>75	nd	29.3	1.19		
	Pregnant women; infant 0–16 mo	Birth length (N=466)	Delivery	<30	nd	50 cm	1.83	0.15	
				30–150	nd	50	2.29		
				50–175	nd	50.5	2.25		
				>75	nd	50.1	2.09		
		Length at 9 mo (N=440)	9 mo	<30	nd	71.2 cm	2.85	0.86	
				30–150	nd	71.4	2.6		
				50–175	nd	71.7	2.89		
				>75	nd	71.1	2.67		
		Height at 9 y (N=178)	9 y	<30	nd	129.6 cm	5.88	0.19	
				30–150	nd	131.5	6.66		
				50–175	nd	131.8	5.09		
				>75	nd	130.6	6.45		

Author Year Study Name PMID	Life Stage	Outcome (n/N; Incidence)	Followup Duration	Maternal 25(OH)D concentration, nmol/L	No. in Category	Final value	Final SD	P value	Study Quality
Radioimmunoassay and chemiluminescence assay averaged together									
Burris 2012[45] and Burris averaged together	Pregnant or lactating women	Birth weight	Delivery	<25	47	3.46kg	SD=0.68	ND	A
				25–150	314	3.55kg	SD=0.52		
				50–175	543	3.53kg	SD=0.51		
				≥75	229	3.51kg	SD=0.52		
HPLC and tandem mass spectrometry									
Gernand 2013[46]	singleton gestation	Birth weight	Delivery	<37.5	747	3127g	SD=15	0.014	B
				≥37.5	1399	3215g	SD=11		

Table 14. Vitamin D and total cancer and total cancer mortality: Characteristics of RCTs [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Radioimmunoassay						
Lappe 2007[102] Nebraska, US (41º N) [17556697]	• Health status • Mean age (SD), y • Male (%)	Mentally and physically fit; post-menopause 67 (7.3) 0	25(OH)D: 71.8 nmol/L	Vit D_3 1000 IU/d + Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. Ca (citrate 1400 mg/d or carbonate 1500 mg/d) vs. placebo	nd	
Other or not reported						
Trivedi 2003[66] Oxford, UK (52°N) [12609940]	• Health status • Mean age (range), y • Male (%)	General population 75 (65–185) 76%	25(OH)D: 53.4 nmol/L Calcium intake= 742 mg/d (at 4 years, no difference by treatment allocation)	Vit D_3 100,000 IU vs. placebo every 4 months	Participants taking ≥80% of study medication: 76%[A]	Previous CVD: 28%, previous cancer: 6%, steroids user: 5%, and HRT taker: 7%

[A]No difference between the vitamin D and the placebo arm.

Table 15. Vitamin D and total cancer and total cancer mortality: Characteristics of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Radioimmunoassay												
Freedman 2007[103] NHANES III US (various) [16481636]	• Health status • Mean age (range), y • Male (%)	Any 44 (≥17) 45	• Assay method • Season blood drawn	RIA (DiaSorin) All	Cancer mortality stratified by prespecified baseline 25(OH)D cut points	X	X	X	X	X	X	Final model includes sex, race/ethnicity, and smoking pattern. Other potential confounders were examined but not chosen.
Melamed 2008[85] NHANES III US (various) [18695076]	• Health status • Mean age (range), y • Male (%)	DM 7.4%, history of CVD 7.9%, HTN 25% 45 (≥20) 46	• Assay method • Season blood drawn	RIA (DiaSorin) All	Cancer mortality stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	
Freedman, 2010[100] US (various)	• Health status • Mean age (SD), y • Male (%)	nd 44.5 87.8%			Total cancer mortality stratified by baseline 25(OH)D sextiles		X	X		X	X	age, race, %female for lowest group of table 1
Tomson 2013[75] Whitehall study London, UK	• Health status • Mean age • Male (%)	Self-reported 76.9 (4.9) 100%			Cancer mortality stratified by baseline 25(OH)D category			X	X		X	
Chemiluminescence Assay												
Eaton, 2011[70] US (various)	• Health status • Mean age (SD), y • Male (%)	nd 65.1 (7.6) 0%			Cancer mortality stratified by baseline 25(OH)D quartiles			X	X	X	X	
Signorello, 2013[74] Southern Community Cohort Study US	• Health status • Mean age (SD), y • Male (%)	nd nd nd						X			X	

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Schottker 2013[76] ESTHER Germany	• Health status • Mean age • Male (%)	NR 62 (SD 6.5) 43.8%		Cancer mortality stratified by baseline 25(OH)D tertiles	X	X		X	X	X	
Afzal 2013[99] Denmark	• Health status • Mean age • Male (%)	NR 58 (47–165) NR		Cancer mortality stratified by baseline 25(OH)D category		X	X			X	
Ordonez-Mena[97] Saarland. Germany	• Health status • Mean age • Male (%)	nd NR (50–174) 54%		Cancer mortality stratified by baseline 25(OH)D tertiles	X	X	X			X	
Enzyme-linked Immunoabsorption Assay											
Hutchinson, 2010[79] Tromso Tromso, Norway	• Health status • Mean age (SD), y • Male (%)	nd nd nd		Cancer mortality stratified by baseline 25(OH)D quartiles		X	X	X		X	
Lin, 2012[83] Linxian, China	• Health status • Mean age (SD), y • Male (%)	Healthy, Hypertension 56.5 (SD 7.9) 55%		Cancer mortality stratified by baseline 25(OH)D tertiles		X	X	X		X	

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
HPLC-Tandem Mass Spectrometry											
Michaelsson, 2010[84] Uppsala Longitudinal Study of Adult Men Uppsala, Sweden	• Health status • Mean age (SD), y • Male (%)	More than 1/3 being treated for hypertension 71 (SD 0.6) 100%		Cancer mortality stratified by baseline 25(OH)D tertiles	X	X	X	X	X	X	Three multivariate models. The most complex model accounted for a range of chronic diseases, supplemental vitamin D use, fish intake, vitamin D intake, C-reactive protein, troponin, triglycerides, HDL cholesterol, retinol, insulin, total energy intake, alcohol intake, lipid lowering treatment, hypertension treatment
Cawthon, 2010[98] MrOS	• Health status • Mean age (range), y • Male (%)	>80% excellent/good health status 74 (≥65) 100%		Cancer mortality stratified by baseline 25(OH)D quartiles and tertiles	X	X	X	X	X	X	MrOS study
de Boer, 2012[87] US (various)	• Health status • Mean age (SD), y • Male (%)	nd 74 (SD 4.6) 30%		Cancer stratified by baseline 25(OH)D median		X	X	X		X	
New Nested case-control study											
Enzyme-linked Immunoabsorption Assay											
Fedirko, 2012[101] EPIC Multiple Countries	• Health status • Mean age (SD), y • Male (%)	nd 62.1 (SD 7.2) 40.5%				X	X	X	X	X	age, %female= quintile 1

Table 16. Vitamin D and total cancer and total cancer mortality: Results of RCTs [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Followup, y	Interventions, Daily Dose	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Radioimmunoassay												
Lappe 2007[102] Nebraska, US (41º N) [17556697]	Post-menopausal women	Incident cancer (all causes)	2°	4	Vit D_3 1000 IU + Ca (citrate 1400 mg or carbonate 1500 mg)	13	446	RR (Vit D+Ca vs. Ca)	0.76	0.38, 1.55	NS	B
					Ca (citrate 1400 mg or carbonate 1500 mg)	17	445					
	Post-menopausal women	Incident cancer (restricted to subjects who were free of cancer at 1 y intervention)	2°	4	Vit D_3 1000 IU + Ca (citrate 1400 mg or carbonate 1500 mg)	8	403	RR (Vit D+Ca vs. Ca)	0.55	0.24,1.28	NS	B
					Ca (citrate 1400 mg or carbonate 1500 mg)	15	416					
Other or not reported												
Trivedi 2003[66] [12609940]	65–185 y, Both sexes	Incident cancer (all causes)	2°	5	Vit D_3 100,000 IU every 4 mo (~833 IU/d)	188	1345	HR (Vit D vs. placebo)	1.09	0.86, 1.36	NS	B
					Placebo	173	1341					
		Total cancer mortality	2°	5	Vit D_3 100,000 IU every 4 mo (~833 IU/d)	63	1345	HR (Vit D vs. placebo)	0.86	0.61, 1.2	NS	
					Placebo	72	1341					

Table 17. Vitamin D and total cancer and total cancer mortality: Results of cohort studies (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
Radioimmunoassay										
Freedman 2007[103] NHANES III US [16481636]	Adults, both sexes	Cancer mortality (536/16818; 0.032)	105 mo	<50	175	5744	**1**	**Reference**	0.65	B
				50 to <62.5	103	3143	1.22	0.91, 1.64		
				62.5 to <80	117	3713	1.02	0.69, 1.50		
				80 to <100	80	4218 (total, ≥80 nmol/L)	1	0.71, 1.40		
				100 to <120	41		0.92	0.58, 1.46		
				≥120	20		1.49	0.85, 2.64		
	Adults, males	Cancer mortality (318/7632; 0.042)	105 mo	<50	88	1993	**1**	**Reference**	0.08	
				50 to <62.5	57	1461	1.03	0.73, 1.44		
				62.5 to <80	71	1845	0.99	0.57, 1.74		
				80 to <100	58	2333 (total, ≥80 nmol/L)	1.21	0.83, 1.78		
				≥100	44		1.35	0.78, 2.31		
	Adults, females	Cancer mortality (218/9163; 0.024)	105 mo	<50	87	3751	**1**	**Reference**	0.12	
				50 to <62.5	46	1682	1.4	0.94, 2.08		
				62.5 to <80	46	1845	1.02	0.62, 1.67		
				80 to <100	22	1885 (total, ≥80 nmol/L)	0.72	0.40, 1.26		
				≥100	17		0.78	0.40, 1.53		
Melamed 2008[85] NHANES III US (various) [18695076]	Adults, both sexes	Cancer mortality (N=13331)	Median 8.7 (IQR 7.1–110.2) y	>80	nd	nd	**1**	**Reference**	nd	C
				61–180	nd	nd	0.8	0.54, 1.19		
				44–160	nd	nd	1.08	0.8, 1.46		
				<44	nd	nd	0.91	0.63, 1.31		

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
Freedman 2010[100] NHANES III US (multisite)	men & women, all seasons	total cancer mortality	13.4 yrs	< 37.5 nmol/L	116	2689	RR = 1	Reference	0.43	
				37.5–1<50 nmol/L	174	3056	1.04	0.77, 1.41		
				50–<62.5 nmol/L	165	3143	1.23	0.89, 1.69		
				62.5–180 nmol/L	200	3713	1.19	0.86, 1.65		
				80–1<100 nmol/L	139	2521	1.12	0.80, 1.57		
				≥100 nmol/L	90	1697	1.15	0.79, 1.68		
	men & women, winter/lower latitude	total cancer mortality		< 37.5 nmol/L	55	2689	1.00	Reference	0.23	
				37.5–1<50 nmol/L	79	3056	1.3	0.77, 2.19		
				50–<62.5 nmol/L	57	3143	1.2	0.64, 2.26		
				62.5–180 nmol/L	78	3713	1.67	0.98, 2.86		
				80–1<100 nmol/L	54	2521	1.31	0.77, 2.23		
				≥100 nmol/L	32	1697	1.5	0.74, 3.02		B
	men & women, summer/ higher latitude			< 37.5 nmol/L	61	2689	1.00	Reference	0.67	
				37.5–1<50 nmol/L	95	3056	0.91	0.63, 1.32		
				50–<62.5 nmol/L	108	3143	1.19	0.78, 1.82		
				62.5–180 nmol/L	122	3713	1.02	0.67, 1.54		
				80–1<100 nmol/L	85	2521	1.03	0.66, 1.63		
				≥100 nmol/L	58	1697	1.02	0.63, 1.45		
	men, all seasons			< 37.5 nmol/L	47	2689	1.00	Reference	0.09	
				37.5–1<50 nmol/L	95	3056	1.66	0.98, 2.80		
				50–<62.5 nmol/L	90	3143	1.43	0.90, 2.26		
				62.5–180 nmol/L	122	3713	1.52	0.82, 2.80		
				80–1<100 nmol/L	90	2521	1.66	1.06, 2.61		
				≥100 nmol/L	69	1697	1.85	1.02, 3.35		
	men, winter/lower latitude			< 37.5 nmol/L	25	2689	1.00	Reference	0.55	
				37.5–1<50 nmol/L	51	3056	2.58	1.37, 4.87		
				50–<62.5 nmol/L	31	3143	1.14	0.48, 2.70		
				62.5-80 nmol/L	52	3713	1.99	0.86, 4.13		
				80-<100 nmol/L	33	2521	1.42	0.74, 2.72		
				≥100 nmol/L	23	1697	1.94	0.69, 5.45		
	men,			< 37.5 nmol/L	22	2689	1.00	Reference	0.045	

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
	summer/higher latitude			37.5-<50 nmol/L	44	3056	1.28	0.51, 3.23		
				50–<62.5 nmol/L	59	3143	1.55	0.81, 2.99		
				62.5–180 nmol/L	70	3713	1.33	0.53, 3.53		
				80–1<100 nmol/L	57	2521	1.76	0.87, 3.57		
				≥100 nmol/L	46	1697	1.84	0.85, 3.98		
	women, all seasons			< 37.5 nmol/L	69	2689	1.00	Reference	0.29	
				37.5–1<50 nmol/L	79	3056	0.85	0.59, 1.22		
				50–<62.5 nmol/L	75	3143	1.25	0.82, 1.90		
				62.5–180 nmol/L	78	3713	1.11	0.69, 1.79		
				80–1<100 nmol/L	49	2521	0.86	0.50, 1.46		
				≥100 nmol/L	21	1697	0.64	0.35, 1.18		
	women, winter/lower latitude			< 37.5 nmol/L	30	2689	1.00	Reference	0.42	
				37.5–1<50 nmol/L	28	3056	0.74	0.36, 1.51		
				50–<62.5 nmol/L	26	3143	1.27	0.51, 3.18		
				62.5–180 nmol/L	26	3713	1.44	0.61, 3.38		
				80–1<100 nmol/L	21	2521	1.28	0.50, 3.24		
				≥100 nmol/L	9	1697	1.01	0.26, 3.90		
	women, summer/higher latitude			< 37.5 nmol/L	39	2689	1.00	Reference	0.03	
				37.5–1<50 nmol/L	51	3056	0.88	0.54, 1.43		
				50–<62.5 nmol/L	49	3143	1.18	0.65, 2.12		
				62.5–180 nmol/L	52	3713	0.99	0.52, 1.87		
				80–1<100 nmol/L	28	2521	0.7	0.34, 1.44		
				≥100 nmol/L	12	1697	0.52	0.25, 1.10		
Tomson 2013[75] Whitehall study		Death, cancer	13.1 yrs	Doubling Concentration	809	5409	0.84	0.71, 1.00		B
Chemiluminescence Assay										
Eaton 2011[70] WHI US (multisite)	Postmenopausal women	cancer mortality	10 yrs	Q 1: 3.25–136.50 nmol/L	nd	608	1.39	0.88, 2.19	0.11	A
				Q 2: 36.51–149.95 nmol/L	nd	606	1.22	0.79, 1.89		
				Q 3: 49.96–165.38 nmol/L	nd	608	1.12	0.72, 1.72		
				Q 4: 65.39–1146.67 nmol/L	nd	607	1.00	Reference		
Signorello 2013[74]	Men and women (40–179 years,	cancer death	NR	Quartile 4: (>54.1 nmol/L)	115	228	OR = 1	Reference	0.53	A

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
Southern Community Cohort Study	2/3 African American)			Quartile 3: 37.9–1>54.1 nmol/L)	102	228	OR = 0.79	0.52, 1.21		
				Quartile 2: (25.45–37.9 nmol/L)	127	255	OR = 1.03	0.66, 1.59		
				Quartile 1: <25.45 nmol/L)	133	243	OR = 1.28	0.78, 2.11		
Schottker 2013[76] ESTHER		cancer mortality	9.5 yrs	<30 30–150 >50	90 172 171	1439 4188 3927	1.42 1.04 1.00	1.08, 1.87 0.83, 1.29 Reference		B
Afzal 2013[99]		all cancer	28 yrs	50% reduction in plasma levels	2488	9791	1.06	1.02, 1.11		B
Ordonez-Mena[97]		total cancer	8 yrs	Q1 Q2+Q3 Q4	235 396 242	2253 4500 2254	1.10 1.00 1.12	0.93, 1.30 Reference 0.95, 1.32		B
Enzyme-linked Immunoabsorption Assay										
Hutchinson 2010[79] Tromsø Study Norway	Men (55–174 years) Women (50–174 years)									
non-smokers		cancer mortality	11.7 yrs	Quartile 1: mean=33.8 (sd=7.6)	72	1184	1.14	0.80–11.63	NR	B
				Quartile 2: mean=46.7 (sd=6.0)	69	1187	1.13	0.80–11.61		
				Quartile 3: mean=56.2 (sd=6.0)	74	1192	1.23	0.87–11.75		
				Quartile 4: mean=72.3 (sd=13.2)	58	1188	1.00	Reference		
smokers				Quartile 1: mean=33.8 (sd=7.6)	55	597	0.82	0.56–11.21	NR	
				Quartile 2: mean=46.7 (sd=6.0)	54	606	0.86	0.59–11.26		
				Quartile 3: mean=56.2 (sd=6.0)	60	607	1.02	0.70–11.48		
				Quartile 4: mean=72.3 (sd=13.2)	56	600	1.00	Reference		
Lin 2012[83] General Population Trial of Linxian China		cancer deaths	24 yrs	continuous 25(OH)D	217	1101	0.97	0.89, 1.05	0.406	B
	Men (40–169 years)			continuous 25(OH)D	141	608	1.00	0.91, 1.10	0.967	
	women			continuous 25(OH)D	76	493	0.88	0.75, 1.03	0.115	

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	25(OH)D, nmol/L	No. of Cases	No. in Category	Adjusted HR	95% CI	P for Trend	Study Quality
HPLC-Tandem Mass Spectrometry										
Michaelsson 2010[84] Uppsala Longitudinal Study of Adult Men Sweden	Elderly men (mean age 71)	cancer mortality	12.7 yrs	< 10th percentile (<46 nmol/L)	27	119	1.99	1.29, 3.08		B
				10th–190th percentile (46–193 nmol/L)	118	956	1.00	Reference		
				>90th percentile (>93 nmol/L)	19	119	1.56	0.95, 2.56		
Cawthon 2010[98] MrOS US (6 sites)	Men 65 and over	cancer mortality	7.3 yrs	Q 1: <49.8 nmol/L	NR	372	0.52	0.27, 1.00	0.086	B
				Q 2: 49.8≥ to <63 nmol/L	NR	370	0.90	0.51, 1.60		
				Q 3: ≥63to <75 nmol/L	NR	372	0.80	0.45, 1.41		
				Q 4: ≥75 nmol/L	NR	376	1.00	reference		
				Deficient, <50 nmol/L	NR	376	0.51	0.27, 0.98	0.044	
				Insufficient, 50 to <75 nmol/L	NR	737	0.85	0.52, 1.40		
				Sufficient, ≥75 nmol/L	NR	377	1.00	reference		
				per SD decrease	NR	1490	0.80	0.64, 0.99	NR	
de Boer 2012[87] Cardiovascular Health Study US (4 sites)	Adults 65 and over	cancer	11 yrs	Normal level	259	1126	1.00	Reference	NR	A
				Low level (season specific, ranges 43–161 nmol/L)	111	495	1.13	0.90, 1.42		
NEW Nested case-control study										
Enzyme-linked Immunabsorption Assay										
Fedirko 2012[101] EPIC Europe (multinational)	Men and women (age at diagnosis approximately 62)	colorectal cancer specific mortality	73 mos	<36.3	104	242	1.00	Reference	0.04	B
				36.4–48.6	85	239	0.76	0.56, 1.02		
				48.7–60.5	95	241	0.93	0.69, 1.24		
				60.6–76.8	78	240	0.78	0.58, 1.06		
				>76.8	82	240	0.69	0.50, 0.93		

* Statistically significant (P<0.05)

Table 18. Vitamin D and prostate cancer: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV Exposure	Life styles	
Cohort Studies												
Radioreceptor Assay												
Corder 1993[114] San Francisco US (37ºN) [8220092]	Health status Mean age (range/SD), y Male (%)	nd 57 (38–81) 100	Assay Season blood drawn	Competitive protein-binding (Haddad, 1971) nd	Prostate cancer risk compared by baseline 25(OH)D		X			X		50% black; 50% white
Nomura 1998[118] Honolulu Heart US (21ºN) [9794175]	Health status Mean age (range/SD), y Male (%)	64% smoked 58 (49–70) 100	Assay Season blood drawn	Protein-binding nd	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X			X	X	100% Japanese Americans
Baron 2005[112] CPP US (multiple latitudes) [15767334][B]	Health status Mean age (range/SD), y Male (%)	had >1 colon adenoma removal 62 (8.7) 100	Assay Season blood drawn	Competitive protein-binding (Quest) nd	Prostate cancer risk stratified by baseline 25(OH)D tertiles	X	X			X		5% black
Radioimmunoassay												
Ahn 2008[110] PLCO US (21ºN to 44ºN) [18505967]	Health status Mean age (range/SD), y Male (%)	8% current smoker 67.8 (5.3) 100	Assay Season blood drawn	RIA (Heartland) nd	Prostate cancer risk stratified by baseline 25(OH)D quintiles	X		X	X		X	
Platz 2004[119] Mikhak 2007[117] HPFS US	Health status Mean age (range/SD), y	Smoked 18%; DM 3.6% 66 (7)	Assay	RIA	Prostate cancer risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	6% nonwhite

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV Exposure	Life styles	
(multiple latitudes) [15090720] [17440943]	Male (%)	100	Season blood drawn	nd								
Freedman 2007[103] NHANES III US (multiple latitudes) [17971526]	Health status Mean age (range/SD), y Male (%)	28% current smoker 44 100	Assay Season blood drawn	RIA South: Nov to Mar; North: Apr to Oct	Prostate cancer mortality stratified by 2 baseline 25(OH)D categories	X	X	X	X	X	X	71% white; 14% black; 6% Hispanics
Tuohimaa 2004[120] Helsinki Heart Vasterbotten; Janus Project; Finland (60°N) [14618623]	Health status Mean age (range/SD), y Male (%)	Gemfibrozil vs. placebo subjects <40 to >60 100	Assay Season blood drawn	RIA (Incstar) nd	Prostate cancer risk stratified by 5 baseline 25(OH)D categories		X			X		
Li 2007[116] Gann 1996[122] PHS US (multiple latitudes) [17388667] [8850273]	Health status Mean age (range/SD), y Male (%)	on ASA, β-carotene, placebo trial; 9% current smoker 58.9 (8.3) 100	Assay Season blood drawn	RIA (Bruce Hollis) 24% spring or winter	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X				X	94% white
Ahonen 2000[111] Helsinki Heart Finland (60°N) [11075874]	Health status Mean age (range/SD), y Male (%)	Gemfibrozil vs. placebo subjects 40–57 100	Assay Season blood drawn	RIA (Incstar) Jan-Feb; Mar-May; Sep	Prostate cancer risk stratified by baseline 25(OH)D quartiles		X	X	X	X	X	
Tuohimaa 2007[121] Helsinki Heart Finland (60°N)	Health status Mean age (range/SD), y	Gemfibrozil vs. placebo subjects 51 (3.7)	Assay	RIA (Incstar)	Prostate cancer risk stratified by 3 baseline 25(OH)D categories		X	X	X			

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demographic	Anthrop	Medical	UV Exposure	Life styles	
17301263	Male (%)	100	Season blood drawn	Most in winter								
Jacobs 2004[115] NPC Eastern US (25º46'N to 41ºN) [15225833]	Health status	Selenium vs. placebo subjects[A]	Assay	RIA	Prostate cancer risk stratified by baseline 25(OH)D tertiles		X	X	X	X	X	
	Mean age (range/SD), y	68 (nd)										
	Male (%)	100	Season blood drawn	nd								
Braun 1995[113] WCC, MD US (39°N) [7612803]	Health status	nd	Assay	RIA (Bruce Hollis, 1993)	Prostate cancer risk stratified by baseline 25(OH)D quintiles		X					100% white
	Mean age (range/SD), y	<45–75+										
	Male (%)	100	Season blood drawn	Aug through Nov								
Nested case-control studies												
Radioimmunoassay												
Shui, 2012[108] Health Professionals' Followup Study US	Health status	nd			Prostate cancer risk stratified by baseline 25(OH)D quartiles	X	X	X	X	X	X	
	Mean age (SD), y	64.4 (SD 7.8)										
	Male (%)	100%										
	Mean age (range/SD), y	73.6 (5.9)										
	Male (%)	100%										
Enzyme-linked Immunoabsorption Assay												
Park, 2010[107] Multiethnic Cohort Study	Health status	nd			Prostate cancer risk stratified by baseline 25(OH)D quartiles	X		X				
	Mean age (SD), y	68.7 (SD 7.2)										
	Male (%)	100%										

Author Year Study Name Location (Latitude) [PMID]	Population		25(OH)D	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demographic	Anthrop	Medical	UV Exposure	Life styles	
Travis 2009[109] European Prospective Investigation into Cancer and Nutrition (EPIC) Multiple Countries	Health status Mean age (SD), y Male (%)	nd 60.5 (SD 6.2) 100%		Prostate cancer risk stratified by baseline 25(OH)D		X	X			X	
Ordonez-Mena 2013[97] ESTHER Saarland, Germany	Health status Mean age Male (%)	NR 50–74 54%		Cancer mortality stratified by baseline 25(OH)D tertiles	X		X	X			confounders- add multivitamin use, fish consumption, red meat consumption, daily fruit intake, daily vegetable intake, scholarly education, physical activity, family history of cancer
HPLC-Tandem Mass Spectrometry											
Barnett, 2010[104] MrOS US (various)	Health status Mean age (range/SD), y Male (%)	nd 73.6 (5.9) 100%		Prostate cancer risk stratified by baseline 25(OH)D quartiles		X			X	X	
Brandstedt, 2012[105] Malmo, Sweden	Health status Mean age (range), y Male (%)	nd 61.7 (NR, SD 6.4) 100%		Prostate cancer risk stratified by baseline 25(OH)D quartiles		X	X			X	Malmo Diet and Cancer Study (MDCS)
Meyer, 2013[106] Norway	Health status Mean age (range), y Male (%)	nd 48.2 (SD 9.2) 100%		Prostate cancer risk stratified by baseline 25(OH)D sextiles		X			X		

[A]For prevention of recurrence of non-melanoma skin cancer.
[B]This is a cohort study, not a nested case-control study.

Table 19. Vitamin D and prostate cancer: Results of observational studies (updated from original report)

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Control)	Time to diagnosis, y	25(OH)D concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
Cohort Studies										
Radioreceptor Assay										
Corder 1993[114]	19–50 51–70	Prostate cancer (181; 181)	>5 (mode)	60.0 (case) vs. 50.5 (control) (est.)	181	181	-	-	-	C
[8220092]		Mortality prostate cancer		nd	51	nd	-	-	-	
Nomura 1998[118]	19–50 51–70	Prostate cancer (136; 136)	16 (mean)	<85[D]	38	34	**1**	**Reference**	0.68	C
Honolulu Heart				85–101	35	36	0.8	0.4, 1.8		
				102–119	30	32	0.8	0.4, 1.7		
[9794175]				≥120	33	34	0.8	0.4, 1.8		
Baron 2005[112] CPP	19–50 51–70	Prostate cancer (70 cases in a total of 672)[F]	<4 (34%)	<62.9	nd	NA	**1**	**Reference**	0.7	C
				62.9–84.9	nd	NA	1.22	0.66, 2.26		
[15767334][F]				85	nd	NA	0.32	0.72, 2.43		
Radioimmunoassay										
Ahn 2008[110]	51–70	Prostate cancer (741; 781)	2–8	12.8–42.5	119	157	**1**	**Reference**	0.2	B
PLCO				42.5–51.	125	156	1.1	0.78, 1.56		
				51.4–60.5	190	157	1.53	1.10, 2.13*		
[8505967]				60.6–71.7	167	156	1.33	0.95, 1.86		
				71.8–129.5	148	155	1.18	0.83, 1.68		
Platz 2004[119] Mikhak 2007[117] HPFS	51–70	Prostate cancer (460; 460)	2.2 (mean)	Quartile 1[A]	109	114	**1**	**Reference**	0.59	B
[15090720]				Quartile 2	115	113	1	0.67, 1.49		
				Quartile 3	94	120	0.77	0.51, 1.15		
[17440943]				Quartile 4	142	113	1.19	0.79, 1.79		
Freedman 2007[103] NHANES III	19–50	Mortality prostate cancer	nd	<62.5	22	nd	**1**	**Reference**	0.95	B
[17971526]				≥62.5	25	nd	0.91	0.39, 2.14		
Tuohimaa 2004[120] Helsinki Heart	19–50 51–70	Prostate cancer (622; 1451)	≤9 –>14 (range)	≤19	19	nd	1.5	0.8, 2.7		C
[14618623]				20–39	169	nd	1.3	0.98, 1.6		
				40–59	229	nd	**1**	**Reference**		
				60–79	138	nd	1.2	0.9, 1.5		
				≥80	67	nd	1.7	1.1, 2.4*		

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Control)	Time to diagnosis, y	25(OH)D concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
Li 2007[116] PHS [17388667]	19–50 51–70	Prostate cancer (492; 664)	11 (median)	Quartile 1[B]	nd	nd	1.01	0.71, 1.44	0.91	C
				Quartile 2	nd	nd	1.26	0.89, 1.80		
				Quartile 3	nd	nd	1	0.71, 1.41		
				Quartile 4	nd	nd	**1**	**Reference**		
Gann 1996[122] PHS [8850273]	19–50 51–70	Prostate cancer (232; 414)	6 (mean)	15.7–53.3	nd	nd	1	nd	0.82	C
				53.4–70.9	nd	nd	1.1	nd		
				71–93.5	nd	nd	1.16	nd		
				93.6–194	nd	nd	0.92	0.56, 1.50		
		Prostate cancer; age ≤61 y		15.7–53.3	nd	nd	1	nd	nd	
				53.4–70.9	nd	nd	1.19	nd		
				71–93.5	nd	nd	1.75	nd		
				93.6–194	nd	nd	1.48	0.73, 2.98		
		Prostate cancer; age >61 y		15.7–53.3	nd	nd	1	nd	nd	
				53.4–70.9	nd	nd	1	nd		
				71–93.5	nd	nd	0.82	nd		
				93.6–194	nd	nd	0.76	0.39, 1.47		
Ahonen 2000[111] Helsinki Heart [11075874]	19–50 51–70	Prostate cancer (149; 566)	8–14 (mode)	< 30[C]	48	131	1.8	1.0, 3.2*	0.01	C
				31–40	41	143	1.4	0.8, 2.4		
				41–54	26	148	0.8	0.5, 1.5		
				> 55	34	144	**1**	**Reference**		
		Prostate cancer in those <52 years old at entry		≤40	nd	nd	3.5	1.7, 7.0*		
				>40	nd	nd	1			
		Prostate cancer in those >51 years old at entry		≤40	nd	nd	1.2	0.7, 2.1		
				>40	nd	nd	1			
Tuohimaa 2007[121] Helsinki Heart [17301263]	19–50 51–70	Prostate cancer (132; 456)	10.8 (mean)	<40	-	-	1.88	1.15, 3.08*		C
				40–59	-	-	**1**	**Reference**		
				≥60	-	-	1.25	0.64, 2.43		
Jacobs 2004[115] NPC [15225833]	51–70	Prostate cancer (83; 166)	5.1 (mean)	20–63.3	26	58	**1**	**Reference**	0.51	C
				63.4–81.9	33	49	1.71	0.68, 4.34		
				82–149	24	59	0.75	0.29, 1.91		

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Control)	Time to diagnosis, y	25(OH)D concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
Braun 1995[113] WCC [7612803]	19–50 51–70	Prostate cancer (61; 122)	14 (mean)	<60.1	7	24	**1**	**Reference**	0.6	C
				60.1–73.8	17	25	2.3	0.7, 7.8		
				73.9–88.5	16	24	2.3	0.7, 7.7		
				88.6–103	4	25	0.6	0.1, 2.5		
				>103	17	24	2.4[E]	0.8, 8.2		
Nested case-control studies										
Radioimmunoassay										
Shui 2012[108] Health Professionals' Followup Study		Lethal Prostate Cancer (209;1324)	5.2 years	Quartile 1	41	325	1.00	**Reference**		A
				Quartile 2	33	336	0.78	0.47, 1.30		
				Quartile 3	21	334	0.50	0.28, 0.88		
				Quartile 4	19	329	0.44	0.24, 0.79	0.002	
		Overall Prostate Cancer (1260;1324)	5.2 years	Quartile 1	310	325	1.00	**Reference**		A
				Quartile 2	298	336	0.93	0.74, 1.17		
				Quartile 3	319	334	0.99	0.79,1.24		
				Quartile 4	333	329	1.07	0.86, 1.34	0.45	
		Advance stage at Diagnosis (166;1324)	5.2 years	Quartile 1	51	325	1.00	**Reference**		
				Quartile 2	43	336	0.96	0.61, 52		
				Quartile 3	32	334	0.63	0.39, 1.03		
				Quartile 4	40	329	0.85	0.53, 1.35	0.22	
		High Grade Prostate Cancer (239;1324)	5.2 years	Quartile 1	69	325	1.00	**Reference**		
				Quartile 2	55	336	0.81	0.54, 1.21		
				Quartile 3	51	334	0.75	0.50, 1.13		
				Quartile 4	64	329	0.99	0.67, 1.46	0.87	
Enzyme-linked Immunoabsorption Assay										
Park 2010[107] multiethnic cohort	Men 45–75 yrs	Prostate Cancer (329, 656)	NR	Quartile 1:<57.3 nmol/L	82	163	1.00	**Reference**		A
				Quartile 2: 57.3 <77.5 nmol/L	84	166	1.05	0.70, 1.58		
				Quartile 3: 77.5<99.8 nmol/L	72	172	0.81	0.52, 1.28		
				Quartile 4: ≥99.8 nmol/L	91	155	1.17	0.72, 1.89	0.600	
				Deficient: <50nmol/LL	53	106	1.10	0.68, 1.78		
				Insufficient: 50–75 nmol/L	98	204	1.04	0.73, 1.48		

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Control)	Time to diagnosis, y	25(OH)D concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
				75–125 nmol/L	137	287	1.00	**Reference**		
				≥125 nmol/L	41	59	1.52	0.92, 2.51	0.320	
Travis 2009[109] European Prospective Investigation into Cancer and Nutrition (EPIC)		Prostate Cancer	4.1 years	Quintile 1 (2.5–40.4nmol/L)	125	151	1.00	**Reference**		A
				Quintile 2(40.5–50.4 nmol/L)	143	150	1.27	0.89, 1.81		
				Quintile 3(50.5–59.1nmol/L)	128	151	1.23	0.85, 1.76		
				Quintile 4 (59.2–70.8nmol/L)	114	150	1.06	0.73, 1.55		
				Quintile 5(70.9–163.7nmol/L)	142	150	1.28	0.88, 1.88		
				Doubling Concentration	652	752	1.17	0.93, 1.47	0.188	
Ordonez-Mena 2013[97] ESTHER		Prostate Cancer	8 yrs	Q1	38	882	HR 1.16	0.78, 1.74		B
				Q2+Q3	66	1737	HR 1.00	**Reference**		
				Q4	67	1505	HR 1.21	0.86, 1.70		
HPLC-Tandem Mass Spectrometry										
Barnett 2010[104] MrOS	men 65 and over	Prostate Cancer (297 cases in a total of 1648)	NR	Quartile 1(7.75–49.75 nmol/L)	68	411	HR=1.00	**Reference**		B
				Quartile 2(50.0–62.3 nmol/L)	91	415	1.35	0.91, 2.01	0.130	
				Quartile 3(62.5–74.8 nmol/L)	53	406	0.64	0.41, 1.00	0.050	
				Quartile 4 (75–189.0 nmol/L)	85	416	1.20	0.81, 1.78	0.370	
Brandstedt 2012[105][HPLC only]	51–70 yrs; ≥71 yrs	Prostate Cancer (918; 924)	NR	Quartile 1(≤68nmol/L)	206	242	1.00	**Reference**		A
				Quartile 2(69–84nmol/L)	237	232	1.25	0.95, 1.65		
				Quartile3(85–102nmol/L)	245	226	1.37	1.03, 1.82		
				Quartile 4(≥103nmol/L)	230	224	1.34	0.99, 1.82	0.048	
Meyer 2013[106]		Prostate Cancer (2106;2106)	NR	<30nmol/L	72	92	IRR=0.82	0.58, 1.15		B
				30–49nmol/L	528	553	1.02	0.87, 1.21		
				50–69nmol/L	718	771	1.00	**Reference**		
				70–89nmol/L	537	466	1.24	1.05, 1.47		
				≥90nmol/L	251	224	1.17	0.93, 1.48		
				30-nmol/L increase	NR	NR	1.13	1.02, 1.25		
				<30nmol/L	49	63	0.80	0.52, 1.23		

Author Year Study Name PMID	Life Stage (male), y	Outcome (No. of Cases; No. of Control)	Time to diagnosis, y	25(OH)D concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
		Prostate Cancer (Winter/Spring)		30–49nmol/L	304	286	1.09	0.86, 1.40		
				50–69nmol/L	288	297	1.00	**Reference**		
				70–89nmol/L	145	128	1.14	0.85, 1.53		
				≥90nmol/L	38	50	0.74	0.46, 1.18		
				30-nmol/L increase	NR	NR	0.97	0.83, 1.14		
		Prostate Cancer (Summer/Autumn)		<30nmol/L	13	14	0.97	0.45, 2.10		
				30–49nmol/L	132	172	0.87	0.66, 1.16		
				50–69nmol/L	296	329	1.00	**Reference**		
				70–89nmol/L	297	259	1.34	1.05, 1.71		
				≥90nmol/L	180	144	1.46	1.07, 2.00		
				30-nmol/L increase	NR	NR	1.25	1.08, 1.45		

*Statistically significant (P<0.05)

[A] Cut points separated by analytical run; season, distributions among control (see Table 3 in original study).
[B] Cut points based on control standardized by season of collection.
[C] Cut points based on total original cohort.
[D] Cut points based on control frequency.
[E] Unadjusted.
[F] This is a cohort study, not a nested case-control study.

Table 26a. Vitamin D and breast cancer: Characteristics of nested case control studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted						Comments
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Radioreceptor Assay and Radioimmunoassay												
Bertone-Johnson 2005[142] NHS US (38º N) [16103450]	• Health status • Mean age (range/SD), y	No Cancer 57 (7.0)	• Assay method • Season blood drawn	RIA All year	Breast cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5	X	X	X	X		X	
Radioimmunoassay												
Freedman 2008[143] PLCO Trial US (38º N) [18381472]	• Health status • Mean age (range/SD), y	No Cancer 67 (ND)	• Assay method • Season blood drawn	RIA Dec-Sep	Breast cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5	X	X	X	X		X	
NEW Studies Chemiluminescence Assay												
Neuhouser 2012[124] WHI US (various)	• Health status • Mean age (SD), y	Post-menopausal 65.1 (SD 6.8)				X	X	X			X	two nested case controls: this one represents the CRC dataset and the one we renumber represents the breast cancer dataset
Engel, 2010[138] French E3N France	• Health outcome • Mean age (SD), y	nd 56.9 (6.4)			Breast cancer risks: Quintile 1 vs. Quintile 2, 3		X	X				
McCullough, 2009[136] Cancer Prevention Study-II (CPS-II)	• Health outcome • Mean age (SD), y	nd 69.6 (5.8)			Breast cancer risks: Quintile 1 vs. Quintile 2, 3, 4, 5		X	X		X		

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Enzyme-linked Immunoabsorption Assay											
Kuhn 2013[145] EPIC Multiple Countries	• Health outcome • Mean age (SD), y	Nd 50.7 (SD 8.8)		Breast Cancer risks: Quintile 1 vs Quintile 2, 3, 4, 5		X	X		X	X	This analysis does not include data from the Malmo site, as these data were analyzed and published separately as Almquist, 2010, reference 126 in the original report.
HPLC-Tandem Mass Spectrometry											
Almquist, 2010[137] Malmo Diet and Cancer Study	• Health outcome • Mean age (SD), y	Healthy 57 (SD 7.3)		Breast cancer risks: Quartile 1 vs. Quartile 2, 3, 4							
Rejnmark, 2009[139] Denmark	• Health outcome • Mean age (SD), y	nd 58 (29–87)		Breast cancer risks: Tertile 1 vs. Tertile 2, 3							

Table 26b. Vitamin D and breast cancer: Characteristics of prospective cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Radioimmunoassay											
Freedman 2007[103] NHANES III US (38º N) [17971526]	• Health status • Mean age (range/SD), y	Non-institutionalized 44 (ND)		Breast cancer risks: Quintile 1 vs. Quintile 2	X	X	X		X	X	
Eliassen, 2011[135] NHSIII	• Health outcome • Mean age (SD), y • Male (%)	nd 44.9 (SD 4.4) 0%		Breast cancer risks: Quartile 1 vs. Quartile 2, 3, 4							
Chemiluminescence Assay											
Jacobs, 2011[144] Women's Healthy Eating and Living (WHEL) US (various)	• Health outcome • Mean age (SD), y • Male (%)	Cancer in remission 51.9 (SD 9) 0%		Breast cancer risks: Quartile 4 vs. Quartile 1, 2, 3							This article contains both prospective cohort and case-control data. Case-control data given here
Ordonez-Mena 2013[97] ESTHER Saarland, Germany	• Health status • Mean age (range/SD), y • Male (%)	nd NR (50–74) 54%		Breast cancer risk: Tertile 2 vs Tertile 1 and 3		X	X			X	confounders– add multivitamin use, fish consumption, red meat consumption, daily fruit intake, daily vegetable intake, scholarly education, physical activity, family history of cancer

Table 27a. Vitamin D and breast cancer: Results of nested case control studies (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Radioreceptor Assay and Radioimmunoassay											
Bertone–Johnson 2005[142] NHS [16103450]	Pre- and Post-menopausal	Breast cancer (701/1425)	<1–82 mo	25(OH)D	≤50 (1st batch)	159	297	**1**	**Reference**	nd	B
					≤70 (2nd batch)						
					≤45 (3rd batch)						
					51–70	149	278	0.95	0.66, 1.36		
					72–85						
					47 to 60						
					72–82	125	266	0.74	0.51, 1.06		
					87–97						
					62–72						
					85–97	144	296	0.8	0.58, 1.11		
					100–117						
					75–90						
					≥100	124	265	0.73	0.49, 1.07		
					≥120						
					≥92						
		Breast cancer <60 y (701/1425)				97	191	**1**	**Reference**	NS	
						84	170	0.96	0.62, 1.49		
						77	164	0.8	0.51, 1.26		
						90	192	0.85	0.55, 1.32		
						70	146	0.92	0.57, 1.48		
		Breast cancer ≥60 y (701/1425)				62	109	**1**	**Reference**	**0.03**	
						65	114	1.07	0.60, 1.92		
						48	105	0.64	0.35, 1.16		
						54	99	0.68	0.38, 1.24		
						54	125	0.57	0.31, 1.04		

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Radioimmunoassay											
Freedman 2008[143] PLCO Cancer Screening Trial [18381472]	Pre- and Post-menopausal	Breast cancer (1005/2010)	12 y	25(OH)D	<46	172	2010	**1**	**Reference**	NS	B
					46-58	188	2010	1.02	0.75, 1.41		
					59-71	244	2010	1.36	0.99, 1.87		
					72-83	205	2010	1.13	0.82, 1.55		
					≥84	196	2010	1.04	0.75, 1.45		
Chemiluminescence Assay											
Neuhouser 2012[124] WHI	50-79 years	Breast Cancer (1080 cases, 1080 controls)	NR	25(OH)D	<36.7	105	181	1.06	0.78, 1.43	0.60	A
					36.7 to <50.9	68	147	1.11	0.83, 1.49		
					50.9 to <64.9	84	162	0.99	0.75, 1.31		
					>64.9	53	130	1.00	**Reference**		
Engel 2010[138] French E3N	born between 1925 and 1950	Breast Cancer (636 cases, 1272 controls)	≤10 years	25(OH)D	<49.5 nmol/L	226	630	OR=1.00	**Reference**		A
					49.5-67.5 nmol/L	198	600	0.81	0.63, 1.04		
					>67.5 nmol/L	191	603	0.73	0.55, 0.96	0.02	
McCullough 2009[136] Cancer Prevention Study-II (CPS-II)	47-85 years	Breast Cancer(516 cases, 516 controls)	1month-6.9 years	25(OH)D	<36.7	89	193	OR=1.00	**Reference**		A
					36.7–49.7	115	217	1.29	0.86, 1.94		
					49.8-60.7	99	204	1.14	0.75, 1.72		
					60.8-73.1	118	220	1.44	0.96, 2.18		
					>73.1	95	198	1.09	0.70, 1,68	0.60	
Enzyme-linked Immunoabsorption Assay											
Kuhn 2013[145] EPIC	40-65 years	Breast Cancer#	4.1 yrs	25(OH)D	Q1: <=39.3	342	688	1.00	**Reference**		A
					Q2: 39.4-50.9	357	707	1.03	0.83, 1.29	0.67	
					Q3: 51.0-63.0	324	670	0.94	0.74, 1.19		
					Q4: >63.0	368	717	1.07	0.85, 1.36		
					log2 (continuous)	1391	2782	1.01	0.86, 1.19	0.86	
HPLC-Tandem Mass Spectrometry											
Almquist 2010[137] Malmo Diet and Cancer	Born 1923-1950	Breast Cancer (213 cases, 213	7.0 years	25(OH)D3	Quartile 1(<70l)	NR	213	OR=1.00	**Reference**		
					Quartile 2 (71-86)	NR	164	0.84	0.60,1.15		

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Study [HPLC only]		controls)			Quartile 3(87-105)	NR	176	0.84	0.60, 1.17		
					Quartile 4(>105)	NR	192	0.93	0.66,1.33	0.71	A
			7.0 years	25(OH)D2+D3	Quartile 1(72)	NR	191	1.00	**Reference**		
					Quartile 2 (72-87)	NR	170	0.95	0.68, 1.31		
					Quartile 3(88-106)	NR	183	0.94	0.68, 1.32		
					Quartile 4(>106)	NR	191	0.96	0.68, 1.37	0.78	
Rejnmark 2009[139]	Pre- and Post-menopausal	Breast Cancer(142 cases, 420 controls)	NR	25(OH)D	<60nmo/L	NR	NR	1.00	**Reference**		
					60-84nmol/L	NR	NR	0.94	0.59, 1.47		B
					>84nmol/L	NR	NR	0.52	0.32, 0.85	<0.05	
	Premenopausal				<60nmo/L	NR	NR	1.00	**Reference**		
					60-84nmol/L	NR	NR	0.59	0.26, 1.33		
					>84nmol/L	NR	NR	0.38	0.15, 0.97	<0.05	
	Postmenopausal				<60nmo/L	NR	NR	1.00	**Reference**		
					60-84nmol/L	NR	NR	1.20	0.67, 2.16		
					>84nmol/L	NR	NR	0.71	0.38, 1.30	>0.05	

*Correlation between two assays evaluated for 20 women: For all samples, the Pearson correlation coefficient between assays was 0.36 (P = 0.12); after the exclusion of two outliers, the correlation was 0.73 (P = 0.0005)
#Total number of women not reported

Table 27b. Vitamin D and breast cancer: Results of prospective cohort studies (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted RR	95% CI	P for Trend	Study Quality
Radioimmunassay											
Freedman 2007[103] NHANES III [17971526]	All Adults	Breast cancer mortality (28/ND)[A]	105 mo	25(OH)D	<63	20	ND	**1**	**Reference**	NS	B
					≥63	8	ND	HR 0.28	0.08, 0.93*		
Eliassen 2011 [135] NHSIII		Breast Cancer (613 cases, 1218 controls)	NR	25(OH)D	Quartile 1(<46 nmol/L)	141	441	1.00	**Reference**		A
					Quartile 2(46.0 to 61.5 nmol/L)	151	456	1.05	0.79, 1.39		
					Quartile 3(61.5 to <76.5 nmol/L)	145	452	0.95	0.71, 1.29		
					Quartile 4 (≥76.5 nmol/L)	176	482	1.20	0.88, 1.63	0.320	
Chemiluminescence Assay											
Jacobs 2011 [144] Women's Healthy Eating and Living (WHEL)		Breast Cancer (512/3085)	NR	25(OH)D	<25 nmol/L(deficient)	nr	51	OR=1.14	0.57, 2.31		B
					≥25and <50 nmol/L(insufficient)	nr	282	1.00	0.68, 1.48		
					≥50 and <75 nmol/L(suboptimal)	nr	410	1.05	0.76, 1.47		
					≥75 nmol/L(optimal)	nr	281	1.00	**Reference**	0.85	
		Premenopausal			<25 nmol/L(deficient)	nr	6	0.17	0.01, 4.56		
					≥25and <50 nmol/L(insufficient)	nr	31	1.02	0.33, 3.16		
					≥50 and <75 nmol/L(suboptimal)	nr	45	1.76	0.64, 4.87		
					≥75 nmol/L(optimal)	nr	36	1.00	**Reference**	0.61	
		Postmenopausal			<25 nmol/L(deficient)	nr	37	1.45	0.62,3.37		
					≥25and <50 nmol/L(insufficient)	nr	202	1.09	0.68, 1.76		
					≥50 and <75 nmol/L(suboptimal)	nr	266	0.90	0.60, 1.36		
					≥75 nmol/L(optimal)	nr	187	1.00	**Reference**	0.49	
Ordonez-Mena 2013[97] ESTHER	50-74 years	Breast Cancer	8 yrs	25(OH)D	Q1	38	1464	1.08	0.72, 1.60		B
					Q2+Q3	71	2951	1.00	Reference		
					Q4	26	846	1.39	0.89, 2.18		

[A] Total number of women not reported.

Table 28. Vitamin D and pancreatic cancer: Characteristics of observational studies (updated from original report)

Author Year Trial/Cohort Country (Latitude) [PMID]	Population		25(OH)D		Comparisons	Confounders/Effect Modifiers Adjusted: Nutrients	Demographic	Anthrop	Medical	UV Exposure	Life styles	Comments
Radioimmunoassay												
Stolzenberg-Solomon 2006[147] ATBC Finland (60°N) [17047087]	Health status Mean age (range/SD), y Male (%)	All smokers 58 100	Assay Season blood drawn	RIA (DiaSorin) nd; but result adjusted for this variable	Exocrine pancreatic risk stratified by baseline 25(OH)D quintiles	X	X			X	X	
Stolzenberg-Solomon 2009[148] PLCO US (various) [19208842]	Health status Mean age (range), y Male (%)	DM: 10.5% 66 (55-74) 65.2	Assay Season blood drawn	RIA (Heartland Assays lab) All seasons	Pancreatic risk stratified by baseline 25(OH)D quintiles Pancreatic risk stratified by residential sun exposure levels and baseline 25(OH)D quartiles		X	X		X	X	
Chemiluminescence Assay												
Stolzenberg-Solomon, 2010 [146] Cohort Consortium Vitamin D Pooling Project or Rarer Cancers	Health status Mean age (SD), y Male (%)	nd nd (nd) 66.5%			Pancreatic risk stratified by baseline 25(OH)D sextiles							
Afzal 2013[99] Denmark	Health status Mean age (SD), y Male (%)	NR 58 (47-65) 45%			Pancreatic risk stratified by baseline 25(OH)D category		X	X			X	HR (95%CI) for pancreatic cancer are shown in Figure 1

Table 29. Vitamin D and pancreatic cancer: Results of observational studies (updated from original report)

Author Year Study Name [PMID]	Life Stage, y	Outcome (No. of Cases; No. of Control)	Time to Diagnosis, y	25(OH)D Concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
Radioimmunoassay										
Stolzenberg-Solomon 2006[147] ATBC Finland (60°N) [17047087]	51-70, male only	Exocrine pancreatic cancer (200; 400)	11.8 (median)	<32	27	80	**1**	**Reference**	0.001	A
				32-41.1	34	80	1.3	0.70, 2.40		
				41.1-51.1	47	80	2.12	1.15, 3.90*		
				51.1-65.5	35	81	1.5	0.81, 2.76		
				>65.5	57	79	2.92	1.56, 5.48*		
Stolzenberg-Solomon 2009[148] PLCO US (various) [19208842]	51-70, both sexes	Pancreatic cancer (184; 368)	5.4 (median), up to 11 y	≤45.9	44	74	**1**	**Reference**	0.49	A
				>45.9 to ≤60.3	40	74	0.97	0.47, 1.98		
				>60.3 to ≤69.5	27	73	0.86	0.40, 1.84		
				>69.5 to ≤82.3	31	74	0.84	0.39, 1.80		
				>82.3	42	73	1.45	0.66, 3.15		
		Pancreatic cancer: Low residential sun exposure area (91; 167)	nd	<49.3	22	44	**1**	**Reference**	P for interaction between low and moderate/high residential sun exposure = 0.015	
				>49.3 to <65.2	22	42	2.52	0.92, 6.90		
				>65.2 to <78.4	21	43	2.33	0.83, 6.48		
				>78.4	26	38	4.03	1.38, 11.79*		
		Pancreatic cancer: Moderate residential sun exposure area (91; 167)	nd	<49.3	33	48	1.97	0.80, 4.82		
				>49.3 to <65.2	15	50	0.66	0.22, 2.01		
				>65.2 to <78.4	18	49	0.91	0.31, 2.71		
				>78.4	24	54	1.45	0.53, 3.96		
Chemiluminescence Assay										
Stolzenberg-Solomon 2010[146] Cohort Consortium Vitamin D Pooling Project or Rarer Cancers		Pancreatic Cancer (952 cases, 1333 controls)	nd	<25	115	256	1.00	**Reference**	0.14	A
				25 to <37.5	164	389	1.04	0.74, 1.44		
				37.5 to <50.0	208	494	1.10	0.79, 1.55		
				50.0 to <75.0	306	764	1.06	0.76, 1.48		
				75.0 to <100.0	120	310	1.08	0.73, 1.59		
				>100	39	69	2.24	1.22, 4.12		

Author Year Study Name [PMID]	Life Stage, y	Outcome (No. of Cases; No. of Control)	Time to Diagnosis, y	25(OH)D Concentration, nmol/L	No. of Cases	No. of Control	Adjusted OR	95% CI	P for Trend	Study Quality
Afzal 2013[99]		Pancreatic Cancer	28 yrs	25(OH)D, 50% reduction in plasma levels	109	9791	HR 1.05	0.84, 1.30		B

* Statistically significant (P<0.05)

Table 30c. Vitamin D and immunologic outcomes: Characteristics of Infectious Disease Continuous RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Radioreceptor assay											
Li-Ng, 2009[150] US Long Island, NY	• Health status • Mean age (range/SD), y • Male (%)	nd 58.1 (SD 13.4) 20.3%		Duration of Upper Respiratory Tract stratified by 25(OH)D levels							
Enzyme-linked Immunoabsorption Assay											
Laaksi, 2010[151] Pori Brigade, Finland	• Health status • Mean age (SD), y • Male (%)	Healthy Nd (nd) 100%		Days absent from duty stratified by 25(OH)D_3 levels		X					

Table 30d. Vitamin D and immunologic outcomes: Characteristics of Infectious Disease Dichotomous RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted						Comments
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle	
Radioreceptor assay											
Li-Ng, 2009[150]	• Health status • Mean age (SD), y • Male (%)	nd 58.1 (SD 13.4) 20.3%		Upper respiratory tract stratified by 25(OH)D medians							
Radioimmunoassay											
Goldring 2013[161] UK	• Health status • Mean age (SD), y • Male (%)	NR 3 44%		Wheeze ever and lower respiratory tract infection stratified by 25(OH)D medians	X	X				X	Children of mothers enrolled in a 3-arm RCT of vitamin D administration were prospectively followed
Chemiluminescence assay											
Manaseki-Holland, 2012[149] Kabul, Afghanistan	• Health status • Mean age (SD), y • Male (%)	nd nd (nd) 52%		Pneumonia stratified by 25(OH)D_3 medians							Age groups reported but not mean age, only father's ethnicity reported
Enzyme-linked Immunoabsorption Assay											
Laaksi, 2010[151] Pori Brigade, Finland	• Health status • Mean age (SD), y • Male (%)	Healthy Nd (nd) 100%		Days absent from duty stratified by 25(OH)D_3 levels		X					
HPLC Tandem Mass Spectrometry											
Murdoch, 2012[152] VIDARIS New Zealand	• Health status • Mean age (SD), y • Male (%)	nd 48 (10) 25%		Days of missed work per episode stratified by 25(OH)D_3 and Placebo medians							
	• Mean age (SD), y • Male (%)	10.4 (2.4) 55%									

Table 31c. Vitamin D and immunologic outcomes: Results of Infectious Disease RCTs-Continuous Outcomes (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration	Intervention	No. Analyzed	Final mean	Final SD	Net Diff	Net Diff 95% CI	Study Quality
Radioreceptor assay										
Li-Ng 2009[150]	18-80 years	Duration of Upper Respiratory Tract	12 wks	Vit D 2000IU/day	78	5.4	4.8	+1.0	-1,2, 1.4	B
				Placebo	70	5.3	3.1	Reference		
Enzyme-linked Immunoabsorption Assay										
Laaksi 2010[151]	18-28 years	Days absent from duty	6 mos	Vit D3 400 IU	80	2.2	3.2	-0.8	-1.9, 0.3	B
				Placebo	84	3.0	4.0	Reference		

Table 31d. Vitamin D and immunologic outcomes: Results of Infectious Disease RCTs-Dichotomous Outcomes (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Intervention	No. of Events	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Radioreceptor assay											
Li-Ng 2009[150]	18-80 years	Upper Respiratory Tract	12 weeks	Vit D	2000IU/day	28	78	OR 0.79	0.41, 1.54	0.61	B
					Placebo	29	70	1	**Reference**		
Radioimmunoassay											
Goldring 2013[161]		wheeze ever	3 yrs	Vit D	either 800 IU ergocalciferol daily or 200,000 IU calciferol (single dose)	11	56	OR 0.56	0.20, 1.57	0.27	A
					control	14	50	OR 1.00	**Reference**		
		lower respiratory tract infection			either 800 IU ergocalciferol daily or 200,000 IU calciferol (single dose)	14	54	OR 1.00	0.35, 2.91	1	

Author Year Study Name [PMID]	Life Stage	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Intervention	No. of Events	No. in Category	Adjusted HR, OR, RR	95% CI	P for Trend	Study Quality
Chemiluminescence assay											
Manaseki-Holland 2012[149]	infants aged 1-11 months	All Pneumonia First episode	NR	Vit D3	100,000IU	260	1782 person years	IRR =1.065	0.895, 1.268	0.476	A
					Placebo	2445	1782 person years	1	**Reference**		
		All Pneumonia repeat episode			100,000IU	138	2031 person years	IRR =1.685	1.282, 2.212	<0.0001	
					Placebo	82	2027 person years	1	**Reference**		
Enzyme-linked immunoabsorption assay											
Laaksi 2010[151]	18-28 years	Self-reported common cold symptoms	6 months	Vit D3	400 IU	45	80	OR 1.17	0.63, 2.16	0.619	B
				Placebo	Placebo	44	84	1	**Reference**		
		No days absent from duty		Vit D3	400 IU	41	80	1.89	1.01, 3.54	0.045	
				Placebo	Placebo	30	84	1	**Reference**		
HPLC Tandem Mass Spectrometry											
Murdoch 2012[152] VIDARIS	18 yrs & older	No. of URTs per person*	18 months	Vit D3 & Placebo	100,000IU	3.7	161	RR =0.97	0.85,1.11	0.65	A
					Placebo	3.7	161	1	**Reference**		
		No. of days if missed work per episode			100,000IU	0.76	161	RR 1.03	0.81, 1.30	0.82	
					Placebo	0.76	161	RR 1	**Reference**		
		Duration of symptoms			100,000IU	12	161	RR 0.96	0.73, 1.25	0.76	
					Placebo	12	161	RR 1	**Reference**		
					control	11	50	OR 1.00	**Reference**		

*Included in Table 31d (dichotomous outcomes) because differences reported as relative risks

Table 32a. Vitamin D and preeclampsia: Characteristics of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted					
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Bodnar 2007[179] PEPPS[A] US (41°N) [17535985]	• Health status • Age range, y • Male (%)	Healthy 20-29 0%	• Assay method • Season blood drawn	ELISA ND	Comparison of mean 25(OH)D levels in cases and controls		x	x			
Radioimmunoassay											
Shand, 2010[177] EMMA Vancouver, Canada	• Health status • Mean age (SD), y • Male (%)	nd nd 0%			Preeclampsia stratified by 25(OH)D medians	X	X	X		X	X
Chemiluminescence Assay											
Wei, 2012[174] International Trial of Antioxidants in the Prevention of Preeclampsia (INTAPP) Canada	• Health status • Mean age (SD), y • Male (%)	31.3% in high-risk group including chronic hypertension, prepregnancy diabetes, multiple pregnancy, or a history of preeclampsia 30.3 (4.8) 0%			Preeclampsia stratified by 25(OH)D tertiles		X	X	X	X	X
Wei 2013[172] INTAPP Canada	• Health status • Mean age (SD), y • Male (%)	nd 28.68 (SD 5.44) 0%			Preeclampsia stratified by 25(OH)D medians		X	X		X	X
Enzyme-linked immunoabsorption assay											
Bodnar 2007[179] PEPPS[A] US (41°N) [17535985]	• Health status • Age range, y • Male (%)	Healthy 20-29 0%	• Assay method • Season blood drawn	ELISA ND	Comparison of mean 25(OH)D levels in cases and controls		x	x			

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
HPLC-Tandem mass Spectrometry										
Baker, 2010[175] US Chapel Hill, NC	• Health status • Mean age (range), y • Male (%)	Healthy 28 (23-34) 0%		Severe preeclampsia stratified by 25(OH)D tertiles		X	X		X	
Powe, 2010[178] US Boston, MA	• Health status • Mean age (SD), y • Male (%)	nd 30.4 (SD 6) 0%		Severe preeclampsia stratified by 25(OH)D quartiles		X			X	
Scholl 2013[173] Camden Study Camden, New Jersey US	• Health status • Mean age (SD), y • Male (%)	Healthy/NR 22.8 (SD 5.4) 0%		Preeclampsia stratified by 25(OH)D quartiles	X	X	X			X
Woodham 2011[176] Chapel Hill, UK	• Health status • Mean age (range), y • Male (%)	nd 29 (25-33) 0%		Severe preeclampsia stratified by 25(OH)D		X	X		X	

[A] Pregnancy Exposures and Preeclampsia Prevention Study

Table 33a. Vitamin D and preeclampsia: Results of observational studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	Study Quality
Radioimmunoassay										
Shand 2010[177]		preeclampsia	10-20 weeks gestation	25(OH)D	<37.5	10	NR	0.91	0.31, 2.62	A
					≥37.5	18	NR	1.00	**Reference**	
					<50	17	NR	1.39	0.54, 3.53	
					≥50	11	NR	1.00	**Reference**	
					<75	21	NR	0.57	0.19, 1.66	
					≥75	6	NR	1.00	**Reference**	
Chemiluminescence Assay										
Wei 2012[174]		preeclampsia	12-18 weeks gestation	25(OH)D	per SD increase	32	697	0.79	0.52, 1.20	A
					<50	15	272	1.24	0.58, 2.67	
					>50	17	425	1.00	**Reference**	
			24-26 weeks gestation		per SD increase	28	604	0.68	0.44, 1.05	
					<50	19	236	3.24	1.37, 7.69	
					>50	9	368	1.00	**Reference**	
Wei 2013[172] INTAPP		preeclampsia	24-26 weeks gestation	25(OH)D	<50 nmol/L	NR	NR	2.97	1.23, 7.20	B
					>=50 nmol/L			1.00	**Reference**	
Enzyme-linked immunoabsorption assay										
Bodnar 2007[179A] PEPPS[B] US (41°N) [17535985]	Pregnancy	Preeclampsia (55/1198; 4%)[C]	ND	25(OH)D[D]	<37.5 (vs. >37.5)	49	265	5	1.7, 14.1	B
HPLC-Tandem mass Spectrometry										
Baker 2010[175]	Pregnant or lactating women	severe preeclampsia	NR	25(OH)D	< 50	22	160	5.41	2.02, 14.52	B
					50-74.9	10	51	2.16	0.85, 5.40	
					≥75	11	30	1.00	**Reference**	

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome (n/N; Incidence)	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	Study Quality
Powe 2010[178]										
					Quartile 1 (ND)	39 (overall)	170 (overall)	1.50	0.57, 3.96	B
		severe preeclampsia	NR	25(OH)D	Quartile 2 (ND)			1.04	0.39, 2.76	
					Quartile 3 (ND)			0.67	0.23, 1.91	
					Quartile 4 (ND)			1.00	**Reference**	
Scholl 2013[173]										
					<30	12	121	2.13	1.07, 4.26	
		preeclampsia	20 weeks gestation	25(OH)D	30-40	12	116	2.09	1.04, 4.22	B
					40-50	7	154	0.94	0.41, 2.17	
					>=50	38	750	1.00	**Reference**	
Woodham 2011[176]		severe preeclampsia	NR	25(OH)D		41	164	0.95	0.94, 0.97	B

[A] This is a nested case-control study.
[B] Pregnancy Exposures and Preeclampsia Prevention Study.
[C] Incidence obtained from the “parent” cohort study in which this case control study is nested.
[D] Early in pregnancy, approximately 30 wk before outcome assessment.

Table 35d. Vitamin D and Bone Health: Characteristics of Observational studies published after the Ottawa EPC report (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Radioimmunoassay						
Cauley, 2008[195] WHI-OS nd	• Health status • Mean age (Range), y • Male (%)	Post-menopausal Nd (50-79) 0%	Serum 25(OH)D controls: 59.60 ± 18.05 nmol/l cases: 55.95 ± 20.28 nmol/l	Quartile 1: 9.2-47.5 nmol/L vs. Quartile 2: 47.6-70.6 nmol/L vs. Quartile 3: 60.2-70.6 nmol/L vs. Quartile 4: 70.7-121.5 nmol/L vs. per 2.5 nmol/L decrease vs. per 25 nmol/L decrease	nd	
Barbour, 2012[194] US Pittsburgh, PA and Memphis, TN	• Health status • Mean age (SD), y • Male (%)	nd nd nd	Dietary calcium intake, median (IQR) (mg/d) 717 (515–973) 736 (532–995) 719 (517–978) 716 (501–940) Supplemental calcium intake (% yes) 18.3 25.0 17.4 28.7 Supplemental vitamin D intake (% yes) 8.3 13.1 8.1 12.2 in order of groups: hip fracture no/yes, any non-spine fracture no/yes	Quartile 1: ≤44.5 nmol/l vs. Quartile 2: 44.5-60.9 nmol/L vs. Quartile 3: 60.9-79.9 nmol/L vs. Quartile 4: >79.9 nmol/L	nd	
Burgi 2011[203] US	• Health status • Mean age (SD), y	nd 19.5 (SD 1.8)	nd	3.8-49.3 nmol/L vs. 49.3-66.5 nmol/L vs.	nd	

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
	• Male (%)	0%		66.5-82.0 nmol/L vs. 82.0-99.5 nmol/L vs. 99.5-281.3 nmol/L		
Cauley 2011[199] WHI OS US	• Health status • Mean age (Range), y • Male (%)	nd 64 (50-70) nd	nd	<50 nmol/L vs. 50-<75 nmol/Ll vs. ≥75 nmol/L	nd	
Looker 2013[196] NHANES III US (multiple cities)	• Health status • Mean age (SD), y • Male (%)	NR 75.2 25.7%	osteoporotic fracture- yes: 57.5 nmol/L, no: 60.1 nmol/L hip fracture- yes: 57.6 nmol/L, 60.0 nmol/L	3 categories per 1 SD unit decline in serum 25OHD	nd	
Chemiluminescence Assay						
Rouzi 2012[200] Jeddah, Saudi Arabia	• Health status • Mean age (SD), y • Male (%)	Healthy 61.3 (SD 7.2) nd	Serum 25(OH)D: 34.27±22.80 nmol/L	<17.90 nmol/L vs. >45.1 nmol/L	nd	
Menant, 2012[193] Sydney, Australia	• Health status • Mean age (SD), y • Male (%)	nd 78 (SD 4.6) Range: 70-90 46%	serum vitamin D- 62.2±24.6 nmol/L	≤ 50nmol/l Vs. > 50nmol/l	nd	
Michael, 2011[189] US (various)	• Health status • Mean age (SD), y • Male (%)	nd 70.3 (SD 3.7) Range: 50-79 0%	Serum vitamin D- 48.2+/-21.4 nmol/L	≥ 75 nmol/l Vs. 50-74nmol/l Vs. 25-49 nmol/l Vs. ≤ 25 nmol/l	nd	

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
HPLC Tandem Mass Spectrometry						
Barrett-Connor, 2012[198] US (various)	• Health status • Mean age (SD), y • Male (%)	Healthy, Overweight/Obese, and diabetes = 10%; mild CKD (GFR<60 mL/min/1.73m3) =12% 74 (SD 6) 100%	nd	Normal level Vs. Low vit D	nd	
de Boer 2012[87] Cardiovascular Health Study US (various)	• Health status • Mean age (SD), y • Male (%)	nd 74.6 (SD 4.6) 30%	Serum vitamin D: 66.2+/-25.8 nmol/L	Normal level Vs. Low level (season specific, ranges 43-61 nmol/L)	nd	
Holvik 2013[197] Norwegian Epidemiologic Osteoporosis Studies (NOREPOS) Norway	• Health status • Mean age (SD), y • Male (%)	46.1-59.2% good or very good health 71.9 (SD 3.9) 28%	median (25th and 75th percentiles) s-25(OH)D in the randomly sampled subcohort was 53.5 (42.2, 67.8) nmol/L	Quartile 1: 4.5-42.1 vs. Quartile 2: 42.2-53.5 vs. Quartile 3: 53.5-67.8 vs. Quartile 4: 67.9-250.0	nd	

Table 36d. Vitamin D and bone health: Results of observational studies published after the Ottawa EPC report (updated from original report)

Author Year Study Name [PMID]	Life Stage	Outcome	1°/ 2°	Mean Followup	Concentration, nmol/L	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Radioimmunoassay												
Cauley, 2008[195] WHI-OS nd		hip fractures	1°	7.1 yrs	Quartile 1: 9.2-47.5 nmol/L	NR	244	OR	1.71	1.05, 2.79		A
					Quartile 2: 47.6-70.6 nmol/L	NR	195		1.09	0.70, 1.71		
					Quartile 3: 60.2-70.6 nmol/L	NR	167		0.82	0.51, 1.31		
					Quartile 4: 70.7-121.5 nmol/L	NR	193		1.00	**Reference**		
					per 2.5 nmol/L decrease	NR	799		1.03	1.01, 1.05	0.015	
					per 25 nmol/L decrease	NR	799		1.33	1.06, 1.68		
Barbour, 2012[194] US Pittsburgh, PA and Memphis, TN	age 70-79	Hip fracture	1°	2 yrs	Quartile 1: ≤44.5 nmol/L	84	2501	HR	1.92	0.97, 3.83	0.217	B
					Quartile 2: 44.5-60.9 nmol/L				0.75	0.32, 1.72		
					Quartile 3: 60.9-79.9 nmol/l				1.86	1.00, 3.45		
					Quartile 4: >79.9 nmol/l				1.00	**Reference**		
		nonspine fracture	1°	2 yrs	Quartile 1: ≤44.5 nmol/L	247	2494	HR	1.21	0.83, 1.75	0.752	
					Quartile 2: 44.5-60.9 nmol/L				1.01	0.68, 1.49		
					Quartile 3: 60.9-79.9 nmol/l				1.12	0.78, 1.60		
					Quartile 4: >79.9 nmol/l				1.00	**Reference**		
Burgi 2011[203] US	9-50 yrs	stress fracture	1°	NR	3.75-49.25 nmol/L	600	1200	OR	1.00	**Reference**	0.02	B
					49.5-66.5 nmol/L				0.77	0.54, 1.11		
					66.8-82 nmol/L				0.76	0.52, 1.10		
					82.3-99.5 nmol/L				0.61	0.42, 0.91		
					99.75-281.25 nmol/L				0.51	0.34, 0.78		
Cauley 2011[199] WHI OS US	Post-menopausal women	fractures	1°	8.6 yrs								
whites					<50 nmol/L	150	270	OR	1.00	**Reference**	0.02	A
					50- <75 nmol/L	156	321		0.82	0.58, 1.16		
					≥75 nmol/L	84	189		0.56	0.35, 0.90		
blacks					<50 nmol/L	241	508	OR	1.00	**Reference**	0.043	
					50- <75 nmol/L	108	193		1.48	1.05, 2.10		
					≥75 nmol/L	30	57		1.33	0.73, 2.43		
Hispanics					<50 nmol/L	89	182	OR	1.00	**Reference**	0.72	
					50- <75 nmol/L	71	140		1.02	0.69, 1.79		
					≥75 nmol/L	31	60		1.09	0.50, 2.37		

Author Year Study Name [PMID]	Life Stage	Outcome	1°/ 2°	Mean Followup	Concentration, nmol/L	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Asians					<50 nmol/L	37	80	OR	1.00	**Reference**	0.22	
					50- <75 nmol/L	45	85		1.49	0.76, 2.93		
					≥75 nmol/L	30	59		1.66	0.68, 4.02		
native Americans					<50 nmol/L	29	55	OR	1.00	**Reference**	0.29	
					50- <75 nmol/L	9	18		0.64	0.15, 2.79		
					≥75 nmol/L	6	15		0.43	0.09, 2.08		
Looker 2013[196] NHANES III		major osteoporotic fracture	1°	7 yrs	per 1 SD unit decline in serum 25OHD	400	4749	RR	1.27	1.12, 1.44		A
						212	NR		1.14	0.97, 1.34		
						188	NR		1.40	1.13, 1.74		
Chemiluminescence Assay												
Rouzi, 2012[200] Jeddah, Saudi Arabia		fragility fractures	1°	5.2 yrs	<17.90 nmol/L	138	707	OR	1.25	0.91, 1.70		A
					>45.1 nmol/L				1.00	**Reference**		
Menant, 2012[193] Sydney, Australia		Primary—Falls in men	1°	1 y	≤ 50nmol/l	94	215	IRR	1.93	1.19, 3.15	0.008	B
					> 50nmol/l			IRR	1.00	**Reference**		
		Primary—Falls in women			≤ 50nmol/l	115	248	IRR	0.83	0.56, 1.23	0.362	
					> 50nmol/l			IRR	1.00	**Reference**		
Michael, 2011[189] US (various)		Primary—Physical performance summary score	1°	6 y								
					≥ 75 nmol/l	NR	64	RR	3.66	1.88, 5.45	<0.001	A
					50-74nmol/l	NR	148	RR	2.32	0.89, 3.75		
					25-49 nmol/l	NR	255	RR	1.64	0.28, 3.01		
					≤ 25 nmol/l	NR	67	RR	1	**Reference**		
HPLC Tandem Mass Spectrometry												
Barrett-Connor, 2012[198] US (various)	51-70 yrs; ≥71 yrs	nonspine fracture	1°	4.6 yrs	Normal level	100	594	HR	1.2	0.8, 1.8		A
					Low vit D	34	183		1.00	**Reference**		
de Boer 2012[87] Cardiovascular Health Study US (various)		Hip fracture	1°	11 yrs	Normal level	118	1126	HR	1.00	Reference	NR	A
					Low level (season specific, ranges 43-61 nmol/L)	72	495		1.34	0.97, 1.84		

Author Year Study Name [PMID]	Life Stage	Outcome	1°/ 2°	Mean Followup	Concentration, nmol/L	N Event	N Total	Outcome Metric (Comparison)	Result	95% CI	P Btw	Study Quality
Holvik 2013[197] Norwegian Epidemiologic Osteoporosis Studies (NOREPOS)		hip fracture	1°	10.7 yrs	Q1: 4.5-42.1	317	256	HR	1.34	1.05, 1.70		A
					Q2: 42.2-53.5	294	255		1.13	0.90, 1.44		
					Q3: 53.5-67.8	272	255		1.10	0.87, 1.39		
					Q4: 67.9-250.0	279	256		1.00	**Reference**		

Table 38. Vitamin D and all-cause mortality: Characteristics of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Vitamin D Concentration		Comparisons	Confounders/Effect Modifiers Adjusted					
						Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Radioreceptor Assay											
Pilz 2009[73] Hoorn Study Netherlands	• Health status • Mean Age (range), y • Male (%)	More than 20% Type 2 Diabetes or impaired glucose tolerance 69.2 (6.5) 50%			All-cause mortality stratified by 25(OH)D quartiles		X	X	X	X	X
Visser 2006[222] Longitudinal Aging Study Netherlands (52°N) [16960177]	• Health status • Age range, y • Male (%)	General population[B] >65 51	• Assay method • Season blood drawn	Competitive protein binding ND	Comparison of various 25(OH)D concentration categories		X	X			X
Radioimmunoassay											
Jia 2007[219] UK (57°N) [17442130]	• Health status • Age range, y • Male (%)	Not terminally ill or demented >75 52	• Assay method • Season blood drawn	RIA ND	Comparison of various 25(OH)D concentration categories		X		X	X	X
Sambrook 2004 & 2006[220,221] FREE[A] Australia (33°S) [15531500 & 16598375]	• Health status • Age range, y • Male (%)	Not bedridden >65 22	• Assay method • Season blood drawn	RIA (Dia-sorin) ND	Association with log 25(OH)D		X		X		
Melamed 2008[85] NHANES III US (various) [18695076]	• Health status • Age mean (range), y • Male (%)	General population 45 (≥20) 46	• Assay method • Season blood drawn	RIA (Dia-sorin) ND	Comparison of various 25(OH)D concentration categories	X	X	X	X	X	X

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Bolland 2010[58] New Zealand	• Health status • Age range, y • Male (%)	Healthy Post-menopausal 74 (SD 4.2) 0%		Comparison of various 25(OH)D concentration categories		X	X	X		X
Johansson 2012[211] MrOS Sweden: Gothenburg, Malmö, Uppsala	• Health status • Mean Age (SD), y • Male (%)	Some with diabetes, htn, cancer, stroke, MI, angina 75.7 (SD 3.4) 100%		Death and mortality stratified by varying 25(OH)D concentration levels		X		X		X
Kritchevsky 2012[212] Health, Aging, and Body Composition (ABC) Study US Pittsburgh, Memphis	• Health status • Mean Age (SD), y • Male (%)	Well-functioning 74.7 (SD 2.9) 49%		All-cause mortality stratified by 25(OH)D quartiles		X	X	X	X	X
Semba 2010[93] InCHIANTI Italy	• Health status • Mean Age (range), y • Male (%)	Nd 78 (72-85) 67.3%		All-cause mortality and cardiovascular mortality stratified by 25(OH)D quartiles		X	X		X	X
Smit 2012[213] NHANES III US (various)	• Health status • Mean Age (SD), y • Male (%)	Malnourished/frailty, pre-frail, not frail 69.4 (SD 0.3) 46.5%		All-cause mortality stratified by 25(OH)D quartiles		X	X	X	X	X
Szulc 2009[214] MINOS Study Montceau les Mines, France	• Health status • Mean Age (SD), y • Male (%)	nd 64 (SD 7) 55%		Mortality stratified by 25(OH)D quartiles	X	X	X	X		X
Szulc 2009[215] MINOS Study Montceau les Mines, France	• Health status • Mean Age (SD), y • Male (%)	nd 64 (SD 7) 100%		Mortality stratified by 25(OH)D quartiles		X	X	X		X

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Tomson 2013[75] Whitehall study London, UK	• Health status • Mean age (SD), y • Male (%)	self-reported health good/excellent 77.4% 76.9 (SD 4.9) 100%		Death (all non-vascular) and Death (al causes) stratified by 25(OH)D doubling concentration			X	X		X
Sempos 2013[218] NHANES III US	• Health status • Mean age (SE), y • Male (%)	NR 45 (SE 0.47) 49%		All-cause mortality stratified by 25(OH)D in 9 categories		X			X	
Formiga 2014[77] Octabaix Spain	• Health status • Mean age (SD), y • Male (%)	Oldest old 85 (SD 0) 39.4%		Total mortality stratified by 25(OH)D quartiles		X		X		
Chemiluminescence Assay										
Eaton 2011[70] WHI substudy US (multisite)	• Health status • Mean Age (SD), y • Male (%)	nd 65.1 (SD 7.6) 0%		Post-menopausal women 50-79 years stratified by 25(OH)D quartiles			X	X	X	X
Jacobs 2011[144] Women's Healthy Eating and Living Well (WHEL) Study	• Health status • Mean Age (SD), y • Male (%)	Cancer in remission 51.9 (SD 9) 0%		Breast cancer survivors stratified by 25(OH)D concentration categories						
Skaaby 2013[86] Monica10 and Inter99 Denmark	• Health status • Mean age (SD), y • Male (%)	NR Monica 10: 55.4 Inter 99: 46.1 Monica 10: 50.2 Inter 99: 49.2		All-cause mortality stratified by 25(OH)D quartiles		X		X	X	X

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
Wong 2013[217] Australia	• Health status • Mean age (SD), y • Male (%)	NR 76 (70-88) 100%		All-cause mortality stratified by 25(OH)D quartiles		X	X	X		X
Schottker 2013[76] ESTHER Germany	• Health status • Mean age (SD), y • Male (%)	NR 62 (SD 6.5) 43.8%		All-cause mortality stratified by 25(OH)D tertiles	X	X		X	X	X
Signorello 2013[74] Southern Community Cohort Study US	• Health status • Mean Age (range), y • Male (%)	nd nd nd		All-cause mortality stratified by 25(OH)D quartiles			X			X
	• Male (%)	100%								
Enzyme-linked Immunoabsorption Assay										
Hutchinson 2010[79] Tromsø Study Tromso, Norway	• Health status • Mean Age (range), y • Male (%)	Nd nd nd		Smoking and non-smoking cause of death stratified by 25(OH)D quartiles		X	X	X		X
Fedirko 2012[101] EPIC US (4 sites)	• Health status • Mean Age (SD), y • Male (%)	nd 62.1 (4.2) 40.5%		Diagnosis at age of 62 stratified by 25(OH)D quintiles		X	X	X	X	X
Lin 2012[83] General Population Trial of Linxian, China	• Health status • Mean Age (SD), y • Male (%)	Healthy, Hypertension 56.5 (7.9) 55%		All-cause mortality stratified by continuous 25(OH)D		X	X	X		X

Author Year Study Name Location (Latitude) [PMID]		Population	Vitamin D Concentration	Comparisons	Confounders/Effect Modifiers Adjusted					
					Nutrients	Demograph	Anthrop	Medical	UV Exposure	Lifestyle
HPLC-Tandem Mass Spectrometry										
Cawthon 2010[98] MrOS (multisite) US	• Health status • Mean age (Age range), y • Male (%)	>80% Excellent/good health status 74 (> or =65) nd		Association with log 25(OH)D	X	X	X	X	X	X
Michaelsson 2010[84] Uppsala Longitudinal Study of Adult Men Uppsala, Sweden	• Health status • Mean Age (range), y • Male (%)	More than 1/3 being treated for hypertension 71 (0.6) 100%		Overall mortality stratified by 25(OH)D tertiles	X	X	X	X	X	X
Kestenbaum 2011[81] Cardiovascular Health Study US (various)	• Health status • Mean Age (range), y • Male (%)	nd 73 (SD 4) 42%		All-cause mortality stratified by 25(OH)D quartiles						
Virtanen 2011[216] Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study Finland	• Health status • Mean Age (range), y • Male (%)	Post-menopausal, 54-62% hypertension 61.8 (53.4-72.7/SD 6.2) 48.6%		Overall mortality stratified by 25(OH)D tertiles		X	X	X		X
Welsh 2012[60] MIDSPAN Family Study Renfrew and Paisley, UK	• Health status • Mean Age (range), y • Male (%)	vitamin D not deficient 45.2 (6.2) 46%		All-cause mortality stratified by 25(OH)D tertiles	X	X	X	X	X	X
de Boer 2012[87] Cardiovascular Health Study US (various)	• Health status • Mean Age (SD), y • Male (%)	[nd] 74 (SD 4.6) 30%		Comparison of various 25(OH)D concentration categories		X	X	X		X

[A]Fracture Risk Epidemiology in the Elderly
[B]~40% with CVD and ~60% arthritis

Table 39. Vitamin D and all-cause mortality: Results of cohort studies (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Radioreceptor Assay											
Pilz 2009[73] Hoorn Study Netherlands	Men and women (50-75 yrs)	all-cause mortality	6.2 yrs	25(OH)D	1st quartile (mean 25(OH)D 30.6 nmol/L)	21	152	HR=1.97	1.08, 3.58	0.027	B
					2nd-4th quartiles (mean 25(OH)D 45.6-78.9)	30	462	1.00	**Reference**		
Visser 2006[222] Longitudinal Aging Study Netherlands (52°N) [16960177]	>65, both sexes	Mortality	72	25(OH)D	<25	66	127	1.28	0.85, 1.92	0.19	C
					25-49.9	42	462	1	0.72, 1.40		
					50-74.9	30	440	0.91	0.65, 1.26		
					≥75	29	231	**1**	**Reference**		
Radioimmunoassay											
Jia 2007[219] UK (57°N) [17442130]	>75, both sexes	Mortality	69	25(OH)D	6.0-23.0 (M)/ 7.0-19.0 (F)	41	75	1.74	0.91, 3.34	0.03	B
					23.1-30.0 (M)/ 29.1-24.0 (F)	34	86	1.4	0.73, 2.70		
					30.1-37.0 (M)/ 24.1-30.2 (F)	21	80	0.9	0.45, 1.79		
					37.1-47.0 (M)/ 30.3-39.0 (F)	17	78	0.8	0.39, 1.62		
					47.1-82.0 (M)/ 39.1-82.0 (F)	16	79	**1**	**Reference**		
Sambrook 2004 & 2006[220,221] FREE[A] Australia (33°S) [15531500 & 16598375]	>65, both sexes	Mortality	27	25(OH)D	NA	559	1112	0.87[B]	0.75, 1.01	nd	C
Melamed 2008[85] NHANES III US (various) [18695076]	>20, both sexes	Mortality	104	25(OH)D	<17.8	nd	nd	1.26	1.08, 1.46	nd	C
					17.8-24.3	nd	nd	1.06	0.89, 1.24		
					24.4-32.1	nd	nd	0.93	0.79, 1.10		
					>32.1	nd	nd	**1**	**Reference**		
	>20, men only	Mortality	104	25(OH)D	<17.8	nd	nd	1.04	0.83, 1.30	nd	C

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
					17.8-24.3	nd	nd	0.94	0.75, 1.19		
					24.4-32.1	nd	nd	0.82	0.64, 1.05		
					>32.1	nd	nd	**1**	**Reference**		
	>20, women only	Mortality	104	25(OH)D	<17.8	nd	nd	1.55	1.15, 1.98	nd	C
					17.8-24.3	nd	nd	1.27	0.97, 1.66		
					24.4-32.1	nd	nd	1.16	0.87, 1.55		
					>32.1	nd	nd	**1**	**Reference**		
	20-65, both sexes	Mortality	104	25(OH)D	<17.8	nd	nd	1.28	0.93, 1.76	nd	C
					17.8-24.3	nd	nd	1.13	0.81, 1.56		
					24.4-32.1	nd	nd	0.81	0.58, 1.14		
					>32.1	nd	nd	**1**	**Reference**		
	³65, both sexes	Mortality	104	25(OH)D	<17.8	nd	nd	1.26	1.03, 1.54	nd	C
					17.8-24.3	nd	nd	0.99	0.82, 1.20		
					24.4-32.1	nd	nd	0.97	0.79, 0.82		
					>32.1	nd	nd	**1**	**Reference**		
Bolland 2010[58] New Zealand	Post-menopausal women	Primary—Death	5 yrs	25(OH)D	<50 nmol/L	13	373	HR=0.90	0.4, 2.0	0.82	A
					≥50 nmol/L	16	366	1.00	**Reference**		
Johansson 2012[211] MrOS (Sweden)	Men (70-81 yrs)	death	8.2 yrs	25(OH)D	per SD decrease	577	2878	HR=1.16	1.06, 1.26	NR	A
Kritchevsky 2012[212] Health, Aging, and Body Composition (ABC) Study	Older community dwelling men and women (70-79 yrs)	all-cause mortality	8.5 yrs	25(OH)D	< 25 nmol/L	44	108	HR=2.27	1.59, 3.24	<0.001	B
					25 to <50 nmol/L	241	750	1.48	1.20, 1.84		
					50 to <75 nmol/L	229	931	1.25	1.02, 1.52		
					≥75 nmol/L	177	849	1.00	**Reference**		
whites		all-cause mortality	8.5 yrs	25(OH)D	< 25 nmol/L	10	25	2.02	1.02, 3.99	0.001	
					25 to <50 nmol/L	82	279	1.54	1.16, 2.06		
					50 to <75 nmol/L	138	620	1.22	0.96, 1.55		
					≥75 nmol/L	143	691	1.00	**Reference**		
blacks		all-cause mortality	8.5 yrs	25(OH)D	<25 nmol/L	34	83	2.59	1.57, 4.26	<0.001	
					25 to <50 nmol/L	159	471	1.76	1.20, 2.57		
					50 to <75 nmol/L	91	311	1.60	1.07, 2.39		

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
					≥75 nmol/L	34	158	1.00	**Reference**		
Semba 2010 [93] InCHIANTI Italy		all-cause mortality	6.5 yrs	25(OH)D	1st quartile: <26.3 nmol/L	NR	252	HR 2.11	1.22, 3.64		
					2nd quartile: 26.3-40.0 nmol/L	NR	254	HR 1.41	0.83, 2.40		
					3rd quartile: 40.3-64 nmol/L	NR	247	HR 1.12	1.09, 1.15		
					4th quartile: >64 nmol/L	NR	253	HR 1.00	**Reference**		
Smit 2012[213] NHANES III	Adults (60 and over)										
	frail	mortality	12 yrs	25(OH)D	Quartile 1: <49.5 nmol/l	NR	NR	2.98	2.01, 4.42		
					Quartile 2: 49.5-66.4 nmol/l	NR	NR	2.37	1.44, 3.89		
					Quartile 3: 66.5-84.1 nmol/l	NR	NR	2.50	1.48, 4.21		
					Quartile 4: >84.1 nmol/l	NR	NR	1.43	0.83, 2.46		
	pre-frail	mortality	12 yrs	25(OH)D	Quartile 1: <49.5 nmol/l	NR	NR	1.97	1.61, 2.40		A
					Quartile 2: 49.5-66.4 nmol/l	NR	NR	1.62	1.29, 2.03		
					Quartile 3: 66.5-84.1 nmol/l	NR	NR	1.51	1.16, 1.97		
					Quartile 4: >84.1 nmol/l	NR	NR	1.82	1.41, 2.35		
	not frail	mortality	12 yrs	25(OH)D	Quartile 1: <49.5 nmol/l	NR	NR	1.25	0.97, 1.60		
					Quartile 2: 49.5-66.4 nmol/l	NR	NR	1.20	0.96, 1.49		
					Quartile 3: 66.5-84.1 nmol/l	NR	NR	1.11	0.88, 1.40		
					Quartile 4: >84.1 nmol/l	NR	NR	1.00	**Reference**		
Szulc 2009[214] MINOS Study	Men(50 yrs and over)	mortality	10 yrs	25(OH)D	per SD decrease	600	782	1.22	1.01, 1.48		A
					Quartile 1 <65 nmol/l summer or <40 nmol/l other months	NR	NR	1.44	1.03, 2.03		
					Quartiles 2-4	NR	NR	1.00	**Reference**		
Szulc 2009[215] MINOS Study	Men(50 yrs and over)	mortality	10 yrs	25(OH)D	Quartile 1	NR	NR	1.6-1.8	NR	<0.05	A
					Quartiles 2-4	NR	NR	1.00	**Reference**		
Tomson 2013[75]		Death,	13.1 yrs	25(OH)D	Doubling Concentration	1857	5409	0.77	0.69, 0.86		B

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Whitehall study		all non-vascular				3215	5409	0.78	0.72, 0.85		
		Death, all causes									
Sempos 2013[218] NHANES III		death from all-cause	15 yrs	25(OH)D	<20	79	251	1.6	1.2, 2.2		A
					20-29	297	1270	1.5	1.2, 1.8		
					30-39	592	2340	1.3	1.1, 1.5		
					40-49	694	2790	1.1	0.96, 1.3		
					50-59	668	2526	1.2	1.01, 1.30		
					60-74	775	3046	1.1	0.99, 1.30		
					75-99	533	2156	1.0	**Reference**		
					100-119	110	518	1.1	0.9, 1.4		
					>=120	36	202	1.4	0.9, 2.2		
Formiga 2014[77] Octabaix		total mortality	2.8 yrs	25(OH)D	Q1: <34.94	15	71	1.28	0.61, 2.6	0.41	B
					Q2: 34.94-61.65	18	77	1.36	0.67, 2.74		
					Q3: 61.66-83.37	11	84	0.76	0.34, 1.68		
					Q4:>83.37	14	80	1.00	**Reference**		
Chemiluminescence Assay											
Eaton 2011[70] WHI substudy US (multisite)	Post-menopausal women 50-79 years	all-cause mortality	10 yrs	25(OH)D	Quartile 1: 3.25-36.50 nmol/L		608	HR=1.25	0.80-1.95	0.39	A
					Quartile 2: 36.51-49.95 nmol/L		606	1.13	0.73-1.75		
					Quartile 3: 49.96-65.38 nmol/L		608	1.17	0.75-1.81		
					Quartile 4: 65.39-146.67 nmol/L		607	1.00	**Reference**		
Jacobs 2011[144] Women's Healthy Eating and Living Well (WHEL) Study	Breast cancer survivors who had completed primary treatment of early stage breast cancer within the previous 4 years	mortality	7.3 yrs	25(OH)D	Insufficient, <50 nmol/L	164		1.13	0.72, 1.79	0.59	B
					Sufficient, ≥50 nmol/L	336		1.00	**Reference**		
Skaaby 2013[86] Monica10 and Inter99		all-cause mortality	10 yrs	25(OH)D	per 10nmol/L			0.95	0.92, 0.99	0.005	B
					Q1	633	8329	1.00	**Reference**	0.041	
					Q2			0.79	0.64, 0.98		
					Q3			0.81	0.65, 1.01		

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
					Q4			0.73	0.57, 0.92		
Wong 2013[217]		all-cause mortality	6.7 yrs	25(OH)D	per 10nmol/L decrease in 25(OH)D	1144	4203	1.04	1.01, 1.07		B
					halving of 25(OH)D			1.21	1.08, 1.35		
					Q1: 10-52.8			1.20	1.02, 1.42		
					Q2: 52.9-67.3			1.00	**Reference**		
					Q3: 67.4-81.6			0.99	0.84, 1.17		
					Q4: 81.7-238.4			0.99	0.83, 1.17		
Schottker 2013[76] ESTHER	>=65 yrs of age	all-cause mortality	9.5 yrs	25(OH)D	<30	238	1444	1.68	1.41, 2.01		B
					30-50	448	4199	1.17	1.01, 1.35		
					>50	397	3935	1.00	**Reference**		
	<65 yrs of age				<30	142	609	1.41	1.13, 1.77		
					30-50	269	1706	1.09	0.90,1.31		
					>50	236	1394	1.00	**Reference**		
					<30	238	835	2.08	1.58, 2.76		
					30-50	448	2493	1.30	1.04, 1.63		
					>50	397	2541	1.00	**Reference**		
Signorello 2013[74] Southern Community Cohort Study US	Men and women (40-79 yrs)	all-cause mortality	1 yr or more	25(OH)D	Quartile 4: (>54.1nmol/L)	364	827	1.00	**Reference**	<0.001	A
					Quartile 3: (37.9-54.1 nmol/L)	405	868	1.17	0.95, 1.45		
					Quartile 2: (25.5-37.9 nmol/L)	482	945	1.41	1.14, 1.74		
					Quartile 1: <25.5 nmol/L)	601	1064	1.80	1.43, 2.27		
African Americans		all-cause mortality	1 yr or more	25(OH)D	Quartile 4: (>54.1nmol/L)	181	400	1.00	**Reference**	0.003	
					Quartile 3: (37.9-54.1 nmol/L)	266	565	1.15	0.87, 1.53		
					Quartile 2: (25.5-37.9nmol/L)	353	730	1.19	0.91, 1.57		
					Quartile 1: <25.5 nmol/L)	475	855	1.60	1.20, 2.14		
non-African Americans		all-cause mortality	1 yr or more	25(OH)D	Quartile 4: (>54.1nmol/L)	179	419	1.00	**Reference**	<0.001	
					Quartile 3: (37.9-54.1 nmol/L)	136	296	1.09	0.78, 1.52		
					Quartile 2: (25.5-37.9 nmol/ L)	129	214	1.99	1.37, 2.90		
					Quartile 1: <25.5 nmol/L)	122	203	2.11	1.39, 3.21		

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
Enzyme-linked Immunoabsorption Assay											
Hutchinson 2010[79] Tromsø Study (Norway)	Men(55-74 yrs) Women (50-74 yrs)	all-cause death	11.7 yrs	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)	247	1184	HR=1.32	1.07-1.62	NR	B
nonsmokers					Quartile 2: mean=46.7 (sd=6.0)	198	1187	1.06	0.86-1.31		
					Quartile 3: mean=56.2 (sd=6.0)	190	1192	1.09	0.88-1.34		
					Quartile 4: mean=72.3 (sd=13.2)	163	1188	1.00	**Reference**		
smokers		all-cause death	11.7 yrs	25(OH)D	Quartile 1: mean=33.8 (sd=7.6)	156	597	1.06	0.83-1.35	NR	
					Quartile 2: mean=46.7 (sd=6.0)	143	606	0.97	0.76-1.25		
					Quartile 3: mean=56.2 (sd=6.0)	138	607	1.04	0.81-1.33		
					Quartile 4: mean=72.3 (sd=13.2)	124	600	1.00	**Reference**		
Fedirko 2012[101] EPIC US (4 sites)	Men and women (diagnosed at an average age of 62)	overall mortality	73 mos	25(OH)D	<36.3	128	242	HR=1.00	**Reference**	<0.01	B
					36.4-48.6	108	239	0.82	0.63, 1.07		
					48.7-60.5	117	241	0.91	0.70, 1.18		
					60.6-76.8	95	240	0.78	0.59, 1.03		
					>76.8	93	240	0.67	0.50, 0.88		
Lin 2012[83] General Population Trial of Linxian (China)		all-cause mortality	24 yrs	25(OH)D	continuous 25(OH)D	793	1101	HR=1.01	0.97, 1.05	0.735	B
	Men 40-69 yrs					479	608	0.99	0.94, 1.04	0.7	
	Women 40-69 yrs					314	493	1.03	0.97, 1.10	0.348	
HPLC-Tandem Mass Spectrometry											
Cawthon 2010[98] MrOS (multisite) US	Men (51-70 yrs; ≥71 years)	all-cause mortality	7.3 yrs	25(OH)D	Quartile 1: <49.75 nmol/L		372	HR=0.95	0.68, 1.34	0.961	B
					Quartile 2: ≥49.75 to <63.0 nmol/L		370	1.05	0.75, 1.47		
					Quartile 3: ≥63.0 to <75.0 nmol/L		372	0.89	0.64, 1.24		

Author Year Study Name Location (Latitude) [PMID]	Age Range, Sex	Outcome	Followup Duration (Time to Dx)	Vit D Measure	Concentration, nmol/L	No. of Cases	No. in Category	Adjusted OR	95% CI	P for Trend	Study Quality
					Quartile 4: ≥75.0		376	1.00	**Reference**		
					Deficient, <50 nmol/L		376	0.94	0.67, 1.32	0.706	
					Insufficient, 50 to <75 nmol/L		737	0.97	0.72, 1.30		
					Sufficient, ≥75 nmol/L		377	1.00	**Reference**		
					per SD decrease			1.01	0.89, 1.14		
Michaelsson 2010[84] Uppsala Longitudinal Study of Adult Men Uppsala (Sweden)	Elderly men birth 1920-1924	overall mortality	12.7 yrs	25(OH)D	< 10th percentile (<46 nmol/L)	76	119	HR=1.43	1.11, 1.84		B
					10th-90th percentile (46-93 nmol/L)	444	956	1.00	**Reference**		
					>90th percentile (>93 nmol/L)	64	119	1.27	0.97, 1.66		
Kestenbaum 2011[81] Cardiovascular Health Study	>65 years	Primary—all-cause mortality	14 yrs	25(OH)D	>75 nmol/L	329	681	HR=1.00	**Reference**		B
					37.5-75.0 nmol/L	668	1247	1.15	1.00, 1.33		
					<37.5 nmol/L	229	384	1.29	1.05, 1.57		
					continuous per 25 nmol/L	1226	2312	1.09	1.02, 1.17	0.012	
Virtanen 2011[216][HPLC alone] Kuopio Ischaemic Heart Disease Risk Factor (KIHD) Study Finland	Men (average age 61.8)	mortality	9.1 yrs	25(OH)D	Tertile 1: 8.9-34.0 nmol/L	39	379	2.06	1.12, 3.80	0.02	A
					Tertile 2: 34.1-50.8 nmol/L	31	378	1.68	0.92, 3.07		
					Tertile 3: 50.9-112.8 nmol/L	17	379	1.00	**Reference**		
Welsh 2012[60] MIDSPAN Family Study Scotland	Men and women	Primary—all-cause mortality	14.4 yrs	25(OH)D	per 1 SD increase	70	1492	0.74	0.56, 0.99		B
					Deficient, <37.5 nmol/L	NR	689	2.02	1.17, 3.51		
					Not deficient ≥37.5 nmol/L	NR	803	1.00	**Reference**		
de Boer 2012[87] Cardiovascular Health Study US (various)	White older adults	Death	11 yrs	25(OH)D	Normal level	539	1126	HR=1.00	**Reference**	NR	A
					Low level (season specific, ranges 43-61 nmol/L)	287	495	1.32	1.14, 1.53		

[A]Fracture Risk Epidemiology in the Elderly
[B]Per unit change in the log-transformed concentration

Table 42. Vitamin D and blood pressure: Characteristics of RCTs (updated from original report)

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
SYSTOLIC BLOOD PRESSURE						
Radioreceptor assay						
Scragg 1995[237] Cambridge, UK (52°N) [7498100]	• Health status • Mean age (range), y • Male (%)	No HTN 70 (63-76) 46%	25(OH)D: 34.5 nmol/L (treatment group), 32.25 nmol/L (control group)	Vit D_3 100,000 IU (2.5 mg) one-time dose vs. Placebo	nd	Complete trial performed in winter
Radioimmunoassay						
Pfeifer 2001[238] Lower Saxony, Germany (52°N) [11297596]	• Health status • Mean age (range), y • Male (%)	Healthy, low Vit D 75 (70-86) 0	25(OH)D < 50 nmol/L	Vit D_3 + Ca supplement vs. Ca supplement	95±12% for the Ca tablets and 96±10% for the Vit D_3 + Ca tablets (pill counting)	
Nagpal 2009[96] New Delhi, India (28.5°N) [19125756]	• Health status • Mean age (SD), y • Male (%)	Healthy, obese 44 (8) 100%	25(OH)D: 36.5 nmol/L (treatment group), 30.0 nmol/L (control group)	Vit D_3 120,000 IU every 2 weeks vs. Placebo	100% (implied); supervised home visits	Excluded subjects who refused subsequent blood draws
DIASTOLIC BLOOD PRESSURE						
Radioreceptor assay						
Scragg 1995[237] Cambridge, UK (52°N) [7498100]	• Health status • Mean age (range), y • Male (%)	No HTN 70 (63-76) 46%	25(OH)D: 34.5 nmol/L (treatment group), 32.25 nmol/L (control group)	Vit D_3 100,000 IU (2.5 mg) one-time dose vs. Placebo	nd	Complete trial performed in winter
Radioimmunoassay						
Pfeifer 2001[238] Lower Saxony, Germany (52°N) [11297596]	• Health status • Mean age (range), y • Male (%)	Healthy, low Vit D 75 (70-86) 0	25(OH)D < 50 nmol/L	Vit D_3 + Ca supplement vs. Ca supplement	95±12% for the Ca tablets and 96±10% for the Vit D_3 + Ca tablets (pill counting)	
Nagpal 2009[96] New Delhi, India	• Health status	Healthy, obese	25(OH)D: 36.5 nmol/L (treatment group), 30.0	Vit D_3 120,000 IU every 2 weeks vs.	100% (implied); supervised home visits	Excluded subjects who refused

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
(28.5°N) [19125756]	• Mean age (SD), y • Male (%)	44 (8) 100%	nmol/L (control group)	Placebo		subsequent blood draws
NEW Studies						
Radioimmunoassay						
Forman 2013[227] Boston, MA	• Health status • Mean age (range), y • Male (%)	Healthy 51 (44-59) 34.6%	Serum vitamin D- 39.3 (26.8-83.5 IQR) nmol/L	Vit D_3 100,000 IU/day Vs. Vit D_3 2000 IU/day Vs. Vit D_3 4000 IU/day Vs. placebo	96.6%	
Jorde 2010[230] Norway	• Health status • Mean age (SD), y • Male (%)	Using blood pressure or lipid lowering medication Overweight/Obese 47.5 (SD 11.4) 35.8%	58.0 ± 21.1 nmol/L	DD (40,000 IU Vit D_3/week)+500 mg calcium/day Vs. DP (20,000 IU Vit D_3/week)+500 mg calcium/day Vs. PP (placebo)+500 mg calcium/day	Vitamin D/placebo capsules 95%-DD group, 96%-DP group and 96%-PP group calcium tablets 82%, 84% and 83%, respectively.	
Enzyme-linked Immunoabsorption Assay						
Salehpour 2012[234] Tehran, Iran	• Health status • Mean age (SD), y • Male (%)	Overweight, obese 38 (SD 8.1) 0%	Serum 25(OH)D Vit D group: 36.8 +/- 30 nmol/l Placebo group - 46.9 +/- 32 nmol/l	Vit D 25 µg/day Vs. placebo	nd	
Witham 2013[235] UK	• Health status • Mean age (SD), y • Male (%)	Healthy 39.4 (SD 11.8) 0%	<50 nmol/L	Vit d3 100,000 units Vs. placebo	nd	

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Toxqui 2013[228] Spain	• Health status • Mean age (SD), y • Male (%)	Healthy 26.5 (SD 3.8) 0%	Serum: D-placebo 62.9 ± 20.8 nmol/L D-fortified 62.3 ± 20.8 nmol/L	vit d 200 IU/day Vs. placebo	>96%	
HPLC-tandem mass spectrometry						
Gepner 2012[229] Madison, WI	• Health status • Mean age (range), y • Male (%)	Healthy Postmenopausal 63.9 (SD 3) 0%	Serum vitamin D- 78.3+/- 26.5 nmol/L	Placebo Vs. Vit D_3 2500 IU/day	nd	
Wood 2012[231] Aberdeen, UK	• Health status • Mean age (range), y • Male (%)	Healthy Post-menopausal 63.9 (SD 2.3) 0%	Serum 25(OH)D placebo: 36.18 ± 17.1 nmol/l 400 IU D3 group: 32.74 ± 12.9 nmol/l 1000 IU D3 group: 32.41 ± 13.8 nmol/l	400 IU Vit D/day Vs. placebo	nd	
Wamberg 2013[236]	• Health status • Mean age (SD), y • Male (%)	Overweight/obese 41.2 (18-50) (SD 6.8) 27%	34.6±10.3 nmol/L	7000 IU cholecalciferol vs. placebo	94±8%	
Not reported						
Zhu 2013[232] Shanghai, China	• Health status • Mean age (range), y • Male (%)	Healthy 20.3 (SD 0.8) 14.3%	Habitual Ca intake CaD group - 426.5 +/- 152.2 mg/d Control group - 392.1 +/- 141.1 mg/d	(energy-restricted diet+600 mg calcium+125 IU Vit D)/day Vs. energy-restricted diet alone (control)	95.8% in the calcium+D group	
Daly 2009[233] Melbourne, Australia	• Health status • Mean age (SD), y	Healthy, obese 61.2 (SD 7.5)	Serum 25(OH)D milk group: 78 ± 23 nmol/l control group: 76 ± 23	(400 ml reduced fact milk fortified with 1000 mg calcium+800 IU Vit	85 ± 21%	

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
	• Male (%)	100%	nmol/l	D)/day Vs. control (no additional fortified milk) (400 ml reduced fact milk fortified with 1000 mg clacium+800 IU Vit D)/day Vs. control (no additional fortified milk)		

Table 43. Vitamin D and blood pressure: Results of RCTs

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
SYSTOLIC BLOOD PRESSURE														
Radioreceptor assay														
Scragg 1995[237] UK [7498100]	63-76 y, Both	SBP	1°	5 wk	Vit D_3 100,000 IU (2.5 mg), 1 dose	95	mm Hg	149	-5	-14.4, 4.4[A]	0	-4.2, 4.2[A]	0.81	A
					Placebo	94		147	-5	-17.9, 7.9[A]				
Radioimmunoassay														
Pfeifer 2001[238] Germany [11297596]	70-86 y, Women	SBP	1°	8 wk	Vit D_3 800 IU +Ca carbonate 1200 mg	73	mm Hg	144.1	-13.1	nd	-7.4	-13.6, -1.2[A]	0.02	B
					Ca carbonate 1200 mg	72		140.6	-5.7	nd				
Nagpal 2009[96] New Delhi, India [19125756]	44 (8, SD) Men	SBP	2°	6 wk	Vit D_3 120,000 IU every 2 wk	35	mm Hg	124	0.6	-2.7, 3.9	4	-0.02, 8.0	0.06	B
					Placebo	36		124	-3.4	-5.8, -1.0				
DIASTOLIC BLOOD PRESSURE														
Radioreceptor assay														
Scragg 1995[237] UK [7498100]	63-76 y, Both	DBP	1°	5 wk	Vit D_3 100,000 IU (2.5 mg), 1 dose	95	mm Hg	82	-1	-6.8, 4.8[A]	0	-2.8, 2.8[A]	0.92	A
					Placebo	94		82	-1	-6.8, 4.8[A]				
Radioimmunoassay														
Pfeifer 2001[238] Germany [11297596]	70-86 y, Women	SBP	1°	8 wk	Vit D_3 800 IU +Ca carbonate 1200 mg	73	mm Hg	84.7	-7.2	nd	-0.3	-0.7, -0.1[A]	0.1	B
					Ca carbonate 1200 mg	72		82.6	6.9	nd				
Nagpal 2009[96] New Delhi, India [19125756]	44 (8, SD) Men	SBP	2°	6 wk	Vit D_3 120,000 IU every 2 wk	35	mm Hg	78	0.4	-2.1, 3.0	1.7	-1.5, 4.9	0.31	B
					Placebo	36		77	-1.3	-3.2, 0.7				

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
NEW Studies														
Radioimmunoassay														
Forman 2013[227] Boston, MA	19-50 yrs	DBP	1°	3 months	Vit D_3 1000 IU/day	68	mm Hg	79.8	final= 78.0	se=1.6[B]	-0.9	-5.7, 3.9	0.71	A
					Vit D_3 2000 IU/day	73		77.6	final= 76.0	se=1.8[B]	-2.9	-7.9, 2.1	0.26	
					Vit D_3 4000 IU/day	70		79.8	final= 78.0	se=1.6[B]	-0.9	-5.7, 3.9	0.71	
					placebo	72		78	final= 78.9	se=1.8[B]				
		SBP			Vit D_3 1000 IU/day	68		124.7	final= 122.5	se=2.0[B]	-2.4	-8.6, 3.8	0.45	
					Vit D_3 2000 IU/day	73		122.8	final= 120.0	se=2.4[B]	-4.9	-11.6, 1.8	0.15	
					Vit D_3 4000 IU/day	70		130.4	final= 126.6	se=2.6[B]	+1.7	-5.3, 8.7	0.63	
					placebo	72		122.2	final= 124.9	se=2.4[B]				
Jorde 2010[230] Norway	19-50, 51-70 yrs	DBP	1°	1 yr	DD (40,000 IU Vit D_3/week)+500 mg calcium/day	114	mm Hg	76.5	change= 1.0	sd=7.4	+0.8	-1.3, 2.9	0.45	B
		DBP			DP (20,000 IU Vit D_3/week)+500 mg calcium/day	104		74.9	change= 1.0	sd=8.3	+0.8	-1.4, 3.0	0.48	
		DBP			PP (placebo)+500 mg calcium/day	112		74.8	change= 0.2	sd=8.3				
		SBP			DD (40,000 IU Vit D_3/week)+500 mg calcium/day	114		124	change= 1.2	sd=11.4	+2.3	-0.9, 5.5	0.15	
		SBP			DP (20,000 IU Vit D_3/week)+500 mg calcium/day	104		121	change= 3.5	sd=11.8	+4.6	1.3, 7.9	<0.001	
		SBP			PP (placebo)+500 mg calcium/day	112		125	change= -1.1	sd=12.8				

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Enzyme-linked Immunoabsorption Assay														
Salehpour 2012[234] Tehran, Iran	19-50 yrs (pre-menopause)	DBP	1°	12 weeks	Vit D 25 µg/day	42	mm Hg	67.9	final= 70.2	sd=8.8	-1.9	-6.1, 2.3	0.37	B
		DBP			placebo	43		71.9	final= 72.1	sd=10.6				
		SBP			Vit D 25 µg/day	42		110.5	final=111	sd=11.3	-3.4	-8.7, 1.9	0.20	
		SBP			placebo	43		116.7	final= 114.4	sd=13				
Witham 2013[235]	≥18 yrs (women)	SBP	2°	8 weeks	Vit d3 100,000 units	25	mm Hg	119	change= 2.0	sd=7.9	+3.0	-1.9, 8.0	0.22	A
		SBP			placebo	25		122	change= -1.0	sd=9.1				
		DBP			Vit d3 100,000 units	25		78	change= -0.1	sd=5.7	+0.6	-2.5, 3.7	0.70	
		DBP			placebo	25		78	change= -0.7	sd=5.2				
Toxqui 2013[228]	18-35 yrs (women)	SBP	2°	16 weeks	vit d 200 IU/day	55	mm Hg	109.3	final= 105.9	sd=9.1	-2.4	-5.9, 1.1	0.178	B
		SBP			placebo	54		107.7	final= 108.3	sd=9.4				
		DBP			vit d 200 IU/day	55		67.1	final= 66.6	sd=7.3	-0.1	-2.9, 2.7	0.944	
		DBP			placebo	54		69.2	final= 66.7	sd=7.5				
HPLC-tandem mass spectrometry														
Gepner 2012[229] Madison, WI	Post-menopause	brachial DBP	2°	4 months	placebo	57	mm Hg	72.6	change= -0.4	sd=4.4				A
		brachial DBP			Vit D_3 2500 IU/day	57		72.45	change= -0.7	sd=5.1	-0.3	-2.1, 1.5	0.73	
		brachial SBP			placebo	57		122.2	change= -2.5	sd=10.9				
		brachial SBP			Vit D_3 2500 IU/day	57		122.3	change= -0.3	sd=8.4	+2.2	-1.4, 5.8	0.23	
		central DBP			placebo	57		73.7	change= -0.5	sd=4.4				
		central DBP			Vit D_3 2500 IU/day	57		73.5	change= -0.7	sd=5.1	-0.2	-2.0, 1.6	0.82	
		central SBP			placebo	57		115.6	change= -2.1	sd=9.7				
		central SBP			Vit D_3 2500 IU/day	57		116.7	change= -0.3	sd=7.0	+1.8	-1.3, 4.9	0.26	

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Wood 2012[231] Aberdeen, UK	Post-menopause	DBP	1°	1 yr	400 IU Vit D/day	97	mm Hg	77.68	change= -2.5	-3.6, -1.4	-0.4	-1.9, 1.1	0.60	A
		DBP			placebo	100		77.7	change= -2.1	-3.1, -1.0				
		SBP			400 IU Vit D/day	96		128.16	change= -2.2	-3.3, -0.7	+0.2	-2.2, 2.6	0.87	
		SBP			placebo	98		128.18	change= -2.4	-4.5, -0.2				
Wamberg 2013[236]	18-50 yrs	SBP	1°	26 weeks	7000 IU cholecalciferol	22	mm Hg	135	final=129	sd=13	-2	-11, 7	0.65	A
		SBP			placebo	21		132	final=131	sd=16				
		DBP			7000 IU cholecalciferol	22		85	final=84	sd=11	0	-7, 7	1	
		DBP			placebo	21		81	final=84	sd=11				
Not reported														
Zhu 2013[232] Shanghai, China	19-50 yrs	DBP	1°	12 weeks	(energy-restricted diet+600 mg calcium+125 IU Vit D)/day	22	mm Hg	70.7	final= 64.2	sd=4.7	-1.2	-4.6, 2.2	0.48	B
		DBP			energy-restricted diet alone (control)	21		70	final= 65.4	sd=6.3				
		SBP			(energy-restricted diet+600 mg calcium+125 IU Vit D)/day	22		119.2	final= 109.6	sd=9.9	-2.3	-8.6, 4.0	0.46	
		SBP			energy-restricted diet alone (control)	21		123	final= 111.9	sd=10.4				
Daly 2009[233] Melbourne, Australia	51-70 yrs	DBP	1°	2 yr	(400 ml reduced fact milk fortified with 1000 mg calcium+800 IU Vit D)/day	66	mm Hg	69.5	change= 4.2	2.1, 6.2	+0.3	-2.6, 3.2	0.84	A
		DBP			control (no additional fortified milk)	58		71	change= 3.9	2.0, 5.8				
		SBP			(400 ml reduced fact milk fortified with 1000 mg clacium+800 IU	66		123.7	change= 6.8	4.2, 9.3	+1.5	-2.4, 5.4	0.45	

Author Year Study Name [PMID]	Age Range, Sex	Outcome	1°/2°	Mean Followup	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
					Vit D)/day									
		SBP			control (no additional fortified milk)	58		120.4	change= 5.3	2.4, 8.2				

[A]Estimated from available data

Table 44. Vitamin D and bone mineral density: Characteristics of RCTs published after the Ottawa EPC report (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Radioreceptor Assay						
Zhu 2008[247] Perth, Australia (32 °S) [18410225]	• Health status • Mean age (SD), y • Male (%)	nd (based on the inclusion and exclusion criteria, assume subjects were not very healthy but normal physical functioning) 77 (4.5) 0	25(OH)D: 44.3 nmol/L Ca: 1097 mg/d	Vit D_2 1000 IU/d + Ca citrate 1200 mg/d vs. Ca citrate 1200 mg/d	86.7% and 86.8% in the vitamin D and the control groups (tablet counting)	
El-Hajj 2006[48] Beirut, Lebanon (33°53'N) [16278262]	• Health status • Mean age (range), y • Male (%)	Healthy 13.2 (10-17) 0	25(OH)D: 34.9 nmol/L Ca: 677 mg/d	Weekly oral Vit D doses of 1400 IU (=Vit D 200 IU/d) or 14,000 IU (Vit D 2000 IU/d) vs. placebo	Placebo - 98%, Low dose group - 98%, High dose group - 97% (pill counting)	
Radioimmunoassay						
Jorde 2010[243] nd	• Health status • Mean age (SD), y • Male (%)	Overweight/Obese 50.8 (10.7) nd	57.7 +/-20.7 nmol/L	DD (Vit D_3 40,000 IU/week+500 mg calcium Vs.) DP (Vit D_3 20,000 IU/week+500 mg calcium) Vs. PP (Placebo+500 mg calcium)	Vitamin D- DD-95%, DP-96%, PP-96%, calcium-82%, 84%, and 83%	
Khadilkar 2010[240] Pune, India	• Health status • Mean age (range), y • Male (%)	nd 14.6 (14.3-15.3) 0%	Vit D + Ca- 24.5 nmol/L (12.7-33.2) Placebo +Ca- 20.8 nmol/L (12.7-30.4)	Vit D_2 300,000 IU x 4 times/year + 250 mg elemental calcium/day Vs. Placebo x 4 times/year + 250 mg elemental calcium/day	nd	
Holmlund-Suila 2012[239] Helsinki, Finland	• Health status • Mean age (range), y • Male (%)	nd Birth 50%	53 nmol/L	Vit D_3 1600 IU/day Vs. Vit D_3 1200 IU/day Vs. Vit D_3 400 IU/day	82% compliance	.

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Nieves 2012[244] New York, US	• Health status • Mean age (SD), y • Male (%)	Vit D deficient/depleted 61.2 (SD 7.6) 0%	Serum 25(OH)D: 29.0±14.3 nmol/L	1,000 IU Vit D_3 Vs. placebo	95%	
Chemiluminescence Assay						
Iuliano-Burns 2012[242] Australiano Antarctic Division	• Health status • Mean age (range), y • Male (%)	Healthy 41 (24-65) 83%	Monthly- 55+/-14 nmol/L Bi-monthly- 60+/-15 nmol/L Single dose-63+/-12 nmol/L	monthly (Vit D_3 50,000 IU/month) vs. bimonthly (Vit D_3 50,000 IU in alternate months) vs. single dose (one does of Vit D_3 50,000 IU pre departure)		
HPLC-Tandem Mass Spectroscopy						
Andersen 2008[246] Copenhagen, Denmark (55 N°) [18208636]	• Health status • Mean age (range), y • Male (%)	Healthy Adolescent girls: 12.2 (10.1-14.7) Women: 36.2 (18.1-52.7) Men: 38.3 (17.9-63.5) 42	25(OH)D: Adolescent girls: 11 nmol/L Women: 12 nmol/L Men: 21 nmol/L Ca: Adolescent girls: 510 mg/d Women: 495 mg/d Men: 548 mg/d	Vit D3 400 IU/d, or Vit D3 800 IU/d vs. placebo	The median compliance was 85 (range 43-100), 92 (42-115) and 93 (33-105)% for girls, women, and men, respectively (pill counting)	Pakistani, living in Denmark. Compliance was lower for girls.
Grimnes 2012[241] Norway	• Health status • Mean age (SD), y • Male (%)	Post-menopausal 63.5 (SD 6.8) 0%	Serum vitamin D: high dose group- 70.7+/-23.0 nmol/L; standard dose group- 71.2+/-22.3 nmol/L	high dose (6500 IU/day)+1000 mg elemental calcium/day vs. standard dose(800 IU/day)+1000 mg elemental calcium/day	97% compliance	
Molgaard 2010[248] Copenhagen and	• Health status	Healthy	Vitamin D intake: pacebo-2.6±1.4ug/d	10 µg Vit D_3/day Vs.	placebo:88±12 5ug/d: 90±10	

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Frederiksberg, Denmark	• Mean age (SD), y • Male (%)	11.4 (SD 0.2) 0%	Serum vitamin D level:placebo-43.4±17.1 nmol/L Calcium intake: placebo-955±588 mg/d	5 µg Vit D_3/day Vs. placebo	10ug/d 88±11	
Macdonald 2013[245] Scotland, UK	• Health status • Mean age (SD), y • Male (%) • Health status • Mean age (SD), y • Male (%)	Healthy, post menopausal 64.6 (SD 2.3) 0%	35.8±16.4 nmol/L	Vit D3 400 IU vs. Vit D3 1000 IU vs. placebo	92% (range 72% to 98%)	

Table 45. Vitamin D and bone mineral density or bone mineral contents: Results of RCTs published after the Ottawa EPC report (updated from original report)

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Radioreceptor Assay														
Zhu 2008[247] Perth, Australia (32 °S) [18410225]	71+. Women only	Hip BMD	1°	12	Vit D_2 1000 IU + Ca citrate 1200 mg	123	mg/cm^2	851	0.50%	-0.09, 1.09	0.30%	nd	NS	A
					Ca citrate 1200 mg	133		826	0.20%	-0.19, 0.59				
El-Hajj 2006[48] Beirut, Lebanon (33°N) [16278262]	10-17 y girls	BMC	1°	12	Vit D 2000 IU	55	kg	1.2	6.20%	4.7, 7.7	0.10%	-1.1, 2.0[C]	NS	C
					Vit D 200 IU	58		1.1	6.10%	4.6, 7.6	1.10%	-0.8, 3.2[C]	NS	
					Placebo	55		1.1	5.00%	3.8, 6.2				
	Subgroup – Premenarchal girls, mean age 10 y	BMC	1°	12	Vit D 2000 IU	14	kg	0.8	11.60%	9.4, 13.8	4.20%	0.7, 7.7[C]	NS	
					Vit D 200 IU	12		0.7	11.40%	9.1, 13.7	4.00%	0.5, 7.5[C]	NS	
					Placebo	8		0.8	7.40%	4.7, 10.1				
Radioimmunoassay														
Jorde 2010[243] nd	19-50, 51-70 yrs	BMD L2-L4	1°	1 yr	DD (Vit D_3 40,000 IU/week+500 mg calcium)	110	g/cm^2	1.27	change= 0.008	sd=0.036	+0.00	-0.01, 0.01	0.85	B
					DP (Vit D_3 20,000 IU/week+500 mg calcium)	97		1.235	change= 0.008	sd=0.039	+0.01	0.0, 0.01	0.86	
					PP (Placebo+500 mg calcium)	105		1.251	change= 0.007	sd=0.042				
		BMD total hip			DD (Vit D_3 40,000 IU/week+500 mg calcium)	110		1.107	change= 0.008	sd=0.014	-0.00	-0.01, 0.0	0.64	
					DP (Vit D_3 20,000 IU/week+500 mg calcium)	97		1.067	change= 0.011	sd=0.014	+0.0	-0.0, 0.01	0.36	
					PP (Placebo+500 mg calcium)	105		1.092	change= 0.009	sd=0.017				
Khadilkar 2010[240] Pune, India	9-18 yrs	L2-L4 bone mineral apparent density	1°	1 yr	Vit D_2 300,000 IU x 4 times/year + 250 mg elemental calcium/day	25	g/cm^3	NR	change= 4.2	0.6, 9.3	+0.5	NC	NC	B
					Placebo x 4 times/year + 250 mg elemental calcium/day	24	g/cm^3	NR	change= 3.7	1.0, 7.7				

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
		L2-L4 BMC			Vit D_2 300,000 IU x 4 times/year + 250 mg elemental calcium/day	25	g	NR	change= 10.5	4.6, 17.2	-0.8	NC	NC	
					Placebo x 4 times/year + 250 mg elemental calcium/day	24	g	NR	change= 11.3	5.4, 18.0				
Holmlund-Suila 2012[239] Helsinki, Finland	0-6 mos	cortical bone density	2°	10 week (age of 3 months)	Vit D_3 1600 IU/day	29	g/cm^3	NR	final=716	se=7	-8	-12.1,-3.9	<0.001	
					Vit D_3 1200 IU/day	28		NR	final=726	se=7	+2	-2.1, 6.1	0.34	
					Vit D_3 400 IU/day	25		NR	final=724	se=8				A
		total and trabecular bone density			Vit D_3 1600 IU/day	29		NR	final=430	se=12	-18	-25, -11	<0.001	
					Vit D_3 1200 IU/day	28		NR	final=451	se=12	+3	-4, 10	0.39	
					Vit D_3 400 IU/day	25		NR	final=448	se=13				
Nieves 2012[244] New York, US	Postmeno-pause	femoral neck BMD	1°	2 yr	1,000 IU Vit D_3	55	g/cm^2	NR	change=-0.2	NR	+0.6	NC	NC	
					placebo	48		NR	change=-0.8	NR				
		spine BMD			1,000 IU Vit D_3	55		1.154	change=-0.5	NR	+0.1	NC	NC	A
					placebo	48		1.212	change=-0.6	NR				
		total hip BMD			1,000 IU Vit D_3	55		1.043	change=-0.5	NR	+0.2	NC	NC	
					placebo	48		1.04	change=-0.7	NR				
		trochanter BMD			1,000 IU Vit D_3	55		NR	change=-0.3	NR	+0.15	NC	NC	
					placebo	48		NR	change= -0.45	NR				
Chemiluminescence Assay														
Iuliano-Burns 2012[242] Australian Antarctic Division	19-50, 0-70 yrs	Femoral neck BMD	1°	up to 12 months (end of expedition)	monthly (Vit D_3 50,000 IU/month)	36	g/cm^2	0.86	final= 0.85	sd=0.13	-0.06	-0.12, 0	0.06	
					bimonthly (Vit D_3 50,000 IU in alternate months)	35		0.82	final= 0.82	sd=0.10	-0.09	-0.15, -0.03	<0.001	B
					single dose (one dose of Vit D_3 50,000 IU pre departure)	31		0.9	final= 0.91	sd=0.13				

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
		Lumbar spine (L1-L4) BMD			monthly (Vit D_3 50,000 IU/month)	36		1	final= 0.98	sd=0.16	-0.09	-0.17, -0.01	0.03	
					bimonthly (Vit D_3 50,000 IU in alternate months)	35		1	final= 1.00	sd=0.09	-0.07	-0.14, -0.0	0.05	
					single dose (one dose of Vit D_3 50,000 IU pre departure)	31		1.08	final= 1.07	sd=0.18				
		Total proximal femur BMD			monthly (Vit D_3 50,000 IU/month)	36		1.02	final= 0.85	sd=0.13	-0.23	-0.30, -0.16	<0.001	
					bimonthly (Vit D_3 50,000 IU in alternate months)	35		1.01	final= 1.01	sd=0.08	-0.07	-0.13, -0.01	0.02	
					single dose (one dose of Vit D_3 50,000 IU pre departure)	31		1.08	final= 1.08	sd=0.15				
		Total BMC			Vit D_2 300,000 IU x 4 times/year + 250 mg elemental calcium/day	25	g	NR	change= 10.1	6.1, 14.7	+1.9	NC	NC	
					Placebo x 4 times/year + 250 mg elemental calcium/day	24	g	NR	change= 8.2	4.9, 12.6				
HPLC-Tandem Mass Spectroscopy														
Andersen 2008[246] Copenhagen, Denmark (55 N°) [18208636]	18-53, Women only	Lumbar spine BMD	1°	12	Vit D_3 400	30/21[A]	mg/cm^2	1.06	0%	nd	-1%	nd	NS	B
					Vit D_3 800	30/21		0.98	1%	nd	0%	nd	NS	
					Placebo	29/18		0.99	1%	nd				
Andersen 2008[246] Copenhagen, Denmark (55 N°) [18208636]	18-64, Men only	Lumbar spine BMD	1°	12	Vit D_3 400	25/19[A]	mg/cm^2	1.03	2%	nd	0%	nd	NS	B
					Vit D_3 800	31/26		0.92	7%	nd	5%	nd	NS	
					Placebo	27/19		1.03	2%	nd				
Andersen 2008[246] Copenhagen, Denmark (55 N°) [18208636]	10-15 y girls	BMC	1°	12	Vit D_3 400	9/7[A]	kg	1.3	22%	nd	7%	nd	NS	C[B]
					Vit D_3 800	7-Sep		1.5	10%	nd	-5%	nd	NS	
					Placebo	7-Aug		1.7	15%	nd				

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Grimnes 2012[241] Norway	Postmeno-pause	Total hip BMD	1°	1 yr	high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm^2	0.79	change= 0.31	sd=1.59	-0.25	-0.63, 0.13	0.19	A
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm^2	0.791	change= 0.56	sd=1.70				
		Femoral neck BMD			high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm^2	0.758	change= 0.03	sd=2.08	-0.14	-0.59, 0.31	0.86	
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm^2	0.757	change= 0.17	sd=1.87				
		L2-L4 BMD			high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm^2	0.901	change= 0.25	sd=3.19	-0.07	-0.80, 0.66	0.85	
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm^2	0.902	change= 0.32	sd=3.23				
		Total Body BMD			high dose (6500 IU/day)+1000 mg elemental calcium/day	149	g/cm^2	1	change= 0.18	sd=1.14	-0.02	-0.29, 0.25	0.88	
					standard dose(800 IU/day)+1000 mg elemental calcium/day	148	g/cm^2	1.002	change= 0.20	sd=1.23				
Molgaard 2010[248] Copenhagen and Frederiksberg, Denmark	9-18 yrs	L1-L4 BMC	1°	12 months	10 µg Vit D_3/day	74	g	28.9	final=36.3	sd=8.6	-1.2	-4.3, 1.9	0.44	B
					5 µg Vit D_3/day	73	g	29.4	final=37.6	sd=10.3	+0.1	-3.2, 3.4	0.95	
					placebo	74	g	29.2	final=37.5	sd=10.2				
		L1-L4 BMD			10 µg Vit D_3/day	74	g/cm^2	0.695	final=0.780	sd=0.113	-0.01	-0.05, 0.03	0.68	
					5 µg Vit D_3/day	73	g/cm^2	0.698	final=0.786	sd=0.115	-0.0	-0.04, 0.04	0.91	
					placebo	74	g/cm^2	0.697	final=0.788	sd=0.121				
		whole body BMD			10 µg Vit D_3/day	74	g/cm^2	0.872	final=0.917	sd=0.080	+0.01	-0.02, 0.03	0.53	
					5 µg Vit D_3/day	73	g/cm^2	0.866	final=0.915	sd=0.075	+0.01	-0.02, 0.03	0.63	
					placebo	74	g/cm^2	0.863	final=0.909	sd=0.075				

Author Year Study Name Location (Latitude) [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Base line	Change/ Final	Change/ Final 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
					10 µg Vit D_3/day	74	g	1308	final=1561	sd=366	+38	-74, 150	0.50	
		whole body BMC			5 µg Vit D_3/day	73	g	1311	final=1559	sd=324	+36	-70, 142	0.50	
					placebo	74	g	1277	final=1523	sd=324				
Macdonald 2013[245]			1°	1 yr	Vit d3 400 IU	83	g/cm2	0.917	final=0.912	sd=0.103	-0.002	-0.036, 0.032	0.91	
		total hip BMD			Vit d3 1000 IU	88		0.923	final=0.923	sd=0.135	+0.009	-0.029, 0.047	0.64	
					placebo	88		0.92	final=0.914	sd=0.118				A
		total lumbar spine BMD			Vit d3 400 IU	83		1.075	final=1.076	sd=0.135	+0.006	-0.038, 0.050	0.79	
					Vit d3 1000 IU	88		1.068	final=1.071	sd=0.164	+0.001	-0.046, 0.048	0.97	
					placebo	88		1.081	final=1.070	sd=0.153				

[A]Baseline/final sample size
[B] Downgraded to C because very small sample size (insufficient power) and no adjustments for confounders
[C]Estimated from available data

Table 65. Combined vitamin D and calcium and bone mineral density/content: Characteristics of RCTs published after the Ottawa EPC report (formerly Table 104) [no new studies in the current report]

Author Year Study Name Location (Latitude) [PMID]		Population	Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Radioreceptor Assay						
Zhu 2008 [266] Beijing, China	• Health status • Mean age (range), y • Male (%)	Healthy 10.1 (SD 0.3) 0%	Vit D intake Control group – 0.9 ± 0.6μg/d CaD milk – 0.9 ± 0.6μg/d	560 mg calcium + 5-8 μg Vit D/school day Vs. control (no supplementary milk and habitual diet)	nd	
Zhu 2008[275] CIFOS Western Australia [18089701]	• Health status • Mean age (SD), y • Male (%)	nd (assumed postmenopausal) 74.8 (2.6) 0	25(OH)D: 68.0 nmol/L Ca: 1010 mg/d	Vit D_2 1000 IU/d + Ca citrate 1200 mg/d vs. placebo	No differences in adherence among groups (81-89% by tablet counting)	
Radioimmunoassay						
Bolton-Smith 2007[274] (UK 54ºN) [17243866]	• Health status • Mean age (range), y • Male (%)	Healthy (assumed postmenopausal) 68 (≥60) 0	25(OH)D: 59.4 nmol/L Ca: 1548 mg/d	Vit D_3 400 IU/d + Elemental Ca 100 mg/d vs. placebo	Good supplement adherence based on pill count (median, 99; IQE 97.3-99.8%).	Noncompliant women were excluded.
Islam 2010[267] Dhaka, Bangladesh	• Health status • Mean age (range), y • Male (%)	Healthy 22.9 (SD 3.9) 0%	placebo-35.0 +/-9.4 nmol/L Vit D-37.1+/-12.1 nmol/L VitD+Ca- 37.8+/-10.9 nmol/L MMN+D+Ca- 36.9+/-12.5 nmol/L	VD (Vit D 10 μg)/day Vs. VD-Ca (Vit D 10 μg + calcium 600 mg)/day Vs. Placebo	compliance not given but 18.5% dropped out	
Jackson 2011[268] WHI US (various)	• Health status • Mean age (range), y • Male (%)	Post menopausal nd 0%	vitamin D intake: placebo- 7.54+/-6.36 ug/d, CaD- 7.42+/-5.84 ug/d calcium intake: placebo- 1049+/-625.7 mg/d, CaD- 1,039+/-635.1 mg/d	(400 IU Vit D_3+1000 mg elemental calcium)/day Vs. placebo	80% or greater compliance-968 women (placebo = 500, CaD= 468)	
Karkkainen 2010[269] OSTPRE-FPS Kuopio, Finland	• Health status • Mean age (SD), y • Male (%)	Post menopausal 67.4 (SD 1.9) 0%	intervention- 50.1 (18.8) nmol/l control- 49.2 (17.7) nmol/l (p=0.544)	Vit D 800 IU+calcium 1,000 mg Vs. control (neither supplementation nor placebo)	79% compliance	

Author Year Study Name Location (Latitude) [PMID]	Population		Background Calcium Intake & Vitamin D Data	Comparisons	Compliance	Comments
Kukuljan 2011[272] Geelong, Australia	• Health status • Mean age (range), y • Male (%)	Healthy 59.9 (SD 7.4) 100%	calcium intake: 911–1064 mg/d Serum vitamin D level: 86.3+/-36.0 nmol/L	fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D_3) vs. controls	exercise program- 63% (95% CI: 57, 69) fortified milk- 90% (95% CI, 87, 93),	
Cheng 2005[273] Jyvaskyla, Finland (62°24'N) [16280447]	• Health status • Mean age (range), y • Male (%)	Healthy 11.2 (10-12) 0	Diet Vit D: 100 IU/d Ca: 670 mg/d	Vit D_3 200 IU/d + Ca carbonate 1000 mg/d vs. placebo	65% completed intervention with >50% compliance	
Assay method not reported						
Moschonis 2006[276] Greece (31ºN) [17181890]	• Health status • Mean age (range), y • Male (%)	Postmenopausal 61 (55-65) 0	Diet Vit D: 23.6 IU/d Ca 680 mg/d	Vit D_3 300 IU/d + Ca 1200 mg/d (from low fat dairy products) vs. control (usual diet)	Dairy group 93% (assessed via information obtained at the biweekly sessions	Control group had no intervention (or usual diet) so compliance issue not applicable
Moschonis 2010[270] Postmenopausal Health Study Greece	• Health status • Mean age (SD), y • Male (%)	Healthy 60.7 (SD 5) 0%	Vitamin D intake: 0.61±0.61 ug/d Serum vitamin D level:26.2±8.5 nmol/L Calcium intake: 682.9±226.1 mg/d	(1200 mg calcium+7.5 µg D_3)/day for the first 12 months + (1200 mg calcium+22.5 µg D_3)/day for the next 18 months Vs. control (neither counselling nor dietary products)	nd	
Moschonis 2011[271] Postmenopausal Health Study Greece	• Health status • Mean age (range), y • Male (%)	Healthy 62.4 (SD 5.3) 0%	Vitamin D intake: 0.89±0.66ug/d Calcium intake: 789.6±213.5mg/d	CaD (800 mg calcium+10 µg Vit D_3)/day Vs. control	NR	

Table 66. Combined vitamin D and calcium and bone mineral density/content: Results of RCTs published after the Ottawa EPC report (formerly Table 105) [no new studies in the current report]

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Radioreceptor Assay														
Zhu 2008[266]	9-18 yrs	midriff BMDsc	1°	2 yr	560 mg calcium + 5-8 µg Vit D/school day	112	$mg/cm^{1.5}$ 86	1585	final=1803	sd=446	+43	-79, 165	0.49	B
					control (no supplementary milk and habitual diet)	123	$mg/cm^{1.5}$ 86	1584	final=1760	sd=499				
		pelvis BMDsc			560 mg calcium + 5-8 µg Vit D/school day	112	$mg/cm^{3.0}$ 82	46	final=49	sd=7	0	-1.9, 1.9	1	
					control (no supplementary milk and habitual diet)	123	$mg/cm^{3.0}$ 82	47	final=49	sd=8				
		total body BMDsc			560 mg calcium + 5-8 µg Vit D/school day	112	$mg/cm^{2.5}$ 28	93	final=95	sd=10	+3	0.3, 5.7	0.03	
					control (no supplementary milk and habitual diet)	123	$mg/cm^{2.5}$ 28	95	final=92	sd=11				
Zhu 2008[275] Australia CIFOS [18089701]	Postmenopausal women	Hip BMD	1°	60	Vit D_2 1000 IU + Ca citrate 1200 mg	39/33[B]	mg/cm^2	783	nd		2.20%	1.9, 2.5	0.05	B
					Placebo	41/36[B]		828	nd					
Radioimmunoassay														
Bolton-Smith 2007[274] [17243866]	Postmenopausal women	Femoral neck BMD	nd	24	Vit D_3 400 IU + Elemental Ca 100 mg	50	mg/cm^2	nd	1.9	-6.5, 10.3	1.2	-12.6, 15.0[A]	NS	B
					Placebo	56		nd	0.7	-10.2, 11.6				
Islam 2010[267]		Femoral neck BMC			VD (Vit D 10 µg)/day	40	g	3.384	change=0.061	sd=0.205	+0.14	0.05, 0.22	<0.001	

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
	9-18, 19-50 yrs		1°	1 yr	VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g	3.436	change=0.069	sd=0.174	+0.14	0.07, 0.22	<0.001	A
					Placebo	35	g	3.316	change=-0.075	sd=0.146				
		Femoral neck BMD			VD (Vit D 10 µg)/day	40	g/cm^2	0.8	change=0.012	sd=0.028	+0.02	0.01, 0.03	<0.001	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm^2	0.799	change=0.013	sd=0.030	+0.02	0.01, 0.03	<0.001	
					Placebo	35	g/cm^2	0.768	change=-0.010	sd=0.012				
		Lumbar spine L2-L4 BMC			VD (Vit D 10 µg)/day	40	g	32.548	change=0.620	sd=2.442	+0.58	-0.84, 2.00	0.42	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g	31.782	change=0.687	sd=2.761	+0.65	-0.82, 2.12	0.39	
					Placebo	35	g	32.399	change=0.042	sd=3.673				
		Lumbar spine L2-L4 BMD			VD (Vit D 10 µg)/day	40	g/cm^2	0.898	change=0.013	sd=0.036	+0.02	-0, 0.04	0.12	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm^2	0.895	change=0.010	sd=0.042	+0.01	-0.01, 0.03	0.22	
					Placebo	35	g/cm^2	0.891	change=-0.003	sd=0.049				
		Trochanter BMC			VD (Vit D 10 µg)/day	40	g	5.818	change=0.158	sd=0.549	+0.31	0.09, 0.53	0.01	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g	5.877	change=0.090	sd=0.419	+0.24	0.06, 0.43	0.01	
					Placebo	35	g	5.885	change=-0.151	sd=0.389				
		Trochanter BMD			VD (Vit D 10 µg)/day	40	g/cm^2	0.634	change=0.002	sd=0.021	+0.02	0.01, 0.03	0.002	

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm^2	0.625	change=0.001	sd=0.026	+0.02	0.01, 0.03	0.01	
					Placebo	35	g/cm^2	0.619	change=-0.017	sd=0.029				
		Ward's triangle BMD			VD (Vit D 10 µg)/day	40	g/cm^2	0.654	change=0.010	sd=0.035	+0.03	0.01, 0.04	<0.001	
					VD-Ca (Vit D 10 µg + calcium 600 mg)/day	41	g/cm^2	0.654	change=0.015	sd=0.031	+0.03	0.02, 0.05	<0.001	
					Placebo	35	g/cm^2	0.628	change=-0.018	sd=0.027				
Jackson 2011[268]	Postmenopause	Intertrochanteric BMD	1°	year 6	(400 IU Vit D_3+1000 mg elemental calcium)/day	777	g/cm^2	0.746	final=0.749	sd=0.135	+0.02	0.01, 0.04	<0.001	A
					placebo	751		0.725	final=0.725	sd=0.137				
		Narrow neck BMD			(400 IU Vit D_3+1000 mg elemental calcium)/day	777		0.736	final=0.742	sd=0.133	+0.02	0.01, 0.03	0.003	
					placebo	751		0.723	final=0.722	sd=0.136				
		Shaft BMD			(400 IU Vit D_3+1000 mg elemental calcium)/day	777		1.18	final=1.199	sd=0.189	+0.03	0.01, 0.05	<0.001	
					placebo	751		1.155	final=1.165	sd=0.190				
Karkkainen 2010[269] OSTPRE-FPS	51-70 yrs	Femoral neck BMD	1°	3 yr	Vit D 800 IU+calcium 1,000 mg	280	g/cm^2	0.866	final=0.848	sd=0.13	-0.002	-0.02, 0.02	0.85	C
					control (neither supplementation nor placebo)	311		0.865	final=0.850	sd=0.12				
		Lumbar spine BMD			Vit D 800 IU+calcium 1,000 mg	259		1.039	final=1.047	sd=0.17	0.013	-0.04, 0.02	0.37	

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
					control (neither supplementation nor placebo)	285		1.052	final=1.060	sd=0.17				
		Total body BMD			Vit D 800 IU+calcium 1,000 mg	195		1.069	final=1.078	sd=0.10	-0.003	-0.02, 0.02	0.76	
					control (neither supplementation nor placebo)	238		1.079	final=1.081	sd=0.10				
		Total proximal femur BMD			Vit D 800 IU+calcium 1,000 mg	280		0.948	final=0.934	sd=0.14	-0.005	-0.03, 0.02	0.65	
					control (neither supplementation nor placebo)	310		0.953	final=0.939	sd=0.13				
		Trochanter BMD			Vit D 800 IU+calcium 1,000 mg	280		0.783	final=0.779	sd=0.13	-0.01	-0.03, 0.01	0.31	
					control (neither supplementation nor placebo)	310		0.797	final=0.790	sd=0.13				
		Ward's triangle			Vit D 800 IU+calcium 1,000 mg	280		0.67	final=0.652	sd=0.14	-0.001	-0.02, 0.02	0.93	
					control (neither supplementation nor placebo)	310		0.672	final=0.653	sd=0.13				
Kukuljan 2011[272]		L1-L3 total volumetric BMD	1°	18 months	fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D_3)	45	g/cm^3	164	change=-0.6	-2.1, 0.8	-0.6	-2.7, 1.6	0.61	
	51-70, 71+ yrs				controls	44		171	change=-	-1.5, 1.4				A

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
									0.05					
		L1-L3 trabecular volumetric BMD			fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D_3)	45		115	change=-1.5	-3.1, 0.9	-2.3	-6.4, 1.8	0.26	
					controls	44		120	change=0.8	-2.9, 1.2				
		mid-femur cortical volumetric BMD			fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D_3)	45		1104	change=-1.0	-1.4, -0.6	-0.3	-1.0, 0.4	0.41	
					controls	44		1108	change=-0.7	-1.3, -0.2				
		mid-tibia cortical volumetric BMD			fortified milk (400 ml/day containing 1000 mg calcium+800 IU Vit D_3)	45		1105	change=-1.2	-1.7, -0.7	-0.1	-0.8, 0.6	0.78	
					controls	44		1113	change=-1.1	-1.6, -0.5				
Enzyme-linked Immunoabsorption Assay														
Cheng 2005[273] [16280447]	10-12 y girls	BMC	1°	24	Vit D 200 IU + Ca carbonate 1000 mg	46	kg	1.3	34.70%	34.3%, 35.1 %	-0.3%	-0.8, 0.2[A]	NS	C
					Placebo	39		1.3	35.00%	34.6%, 35.4 %				
Assay method not reported														
Moschonis 2006[276] [17181890]	Postmenopausal women	Total body BMD	1°	12	Vit D_3 300 IU + Ca 1200 mg (from low fat dairy products)	39	mg/cm^2	1.13	1.50%	0.9%, 2.2%	2.20%	1.3, 3.1[A]	<0.05	C
					Control (usual diet)	36		1.12	-0.70%	-1.4%, -0.1 %				
Moschonis 2011[271]		heel BMD	1°	12 months	CaD (800 mg calcium+10 µg Vit D_3)/day	26	g/cm^2	0.476	final=0.459	sd=0.081	-0.002	-0.04, 0.04	0.92	

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
Postmenopausal Health Study	Postmenopause	L2-L4 BMD			control	39		0.472	final=0.461	sd=0.083				B
					CaD (800 mg calcium+10 µg Vit D_3)/day	26		1.121	final=1.113	sd=0.160	+0.01	-0.07, 0.10	0.77	
		total body BMD			control	39		1.134	final=1.101	sd=0.167				
					CaD (800 mg calcium+10 µg Vit D_3)/day	26		1.112	final=1.135	sd=0.083	+0.04	0, 0.08	0.05	
					control	39		1.095	final=1.094	sd=0.079				
Moschonis 2010[270] Postmenopausal Health Study		pelvis BMD	1°	30 months	(1200 mg calcium+7.5 µg D_3)/day for the first 12 months + (1200 mg calcium+22.5 µg D_3)/day for the next 18 months	35	g/cm^2	1.096	final=1.089	sd=0.087	+0.02	-0.02, 0.06	0.30	B
					control (neither counselling nor dietary products)	31		1.067	final=1.067	sd=0.084				
		total body BMD			(1200 mg calcium+7.5 µg D_3)/day for the first 12 months + (1200 mg calcium+22.5 µg D_3)/day for the next 18 months	35		1.134	final=1.135	sd=0.067	+0.03	-0.01, 0.06	0.11	
					control (neither counselling nor dietary products)	31		1.124	final=1.106	sd=0.078				

Author Year Study Name [PMID]	Life Stage	Outcome	1°/2°	Mean Followup, mo	Interventions, Daily Dose	No. Analyzed	Unit	Baseline	Change	Change 95% CI	Net Diff	Net Diff 95% CI	P Btw	Study Quality
		total spine BMD			(1200 mg calcium+7.5 µg D_3)/day for the first 12 months + (1200 mg calcium+22.5 µg D_3)/day for the next 18 months	35		1.119	final=1.234	sd=0.135	+0.04	-0.03, 0.11	0.23	
					control (neither counselling nor dietary products)	31		1.139	final=1.193	sd=0.139				

[A] Estimated from reported data.
[B] Baseline/followup number of subjects analyzed.