Effectiveness of Screening and Treatment of Subclinical Hypo- or Hyperthyroidism

Appendixes

Appendix A

Terminology

Appendix A1. Abbreviations

ACOG	The American College of Obstetricians and Gynecologists
ACP	The American College of Physicians
AHRQ	Agency for Healthcare Research and Quality
BMI	Body Mass Index
CI	Confidence Interval
EHCP	Effective Health Care Program
EPC	Evidence-based Practice Center
HDL	High-density Lipoprotein
kg/m^2	kilograms per meter squared (a measure of body mass index)
KQ	key question
LDL	Low-density Lipoprotein
mcg	microgram
mg/dL	milligrams per deciliter

mIU/L	milli-international units per liter
mIU/L^2	milli-international units per liter squared
mmHg	millimeters of mercury
ng/dl	nanograms per deciliter
PICOTS	Population, Intervention, Comparators, Outcome, Timing, and Setting
RCT	Randomized Controlled Trial
SIP	Scientific Information Packet
TPO	Thyroid Peroxidase
TSH	Thyroid Stimulating Hormone
T3	Triiodothyronine
T4	Thyroxine
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

Appendix B

Detailed Methods

FIGURE B1A. Systematic Review Literature flow diagram

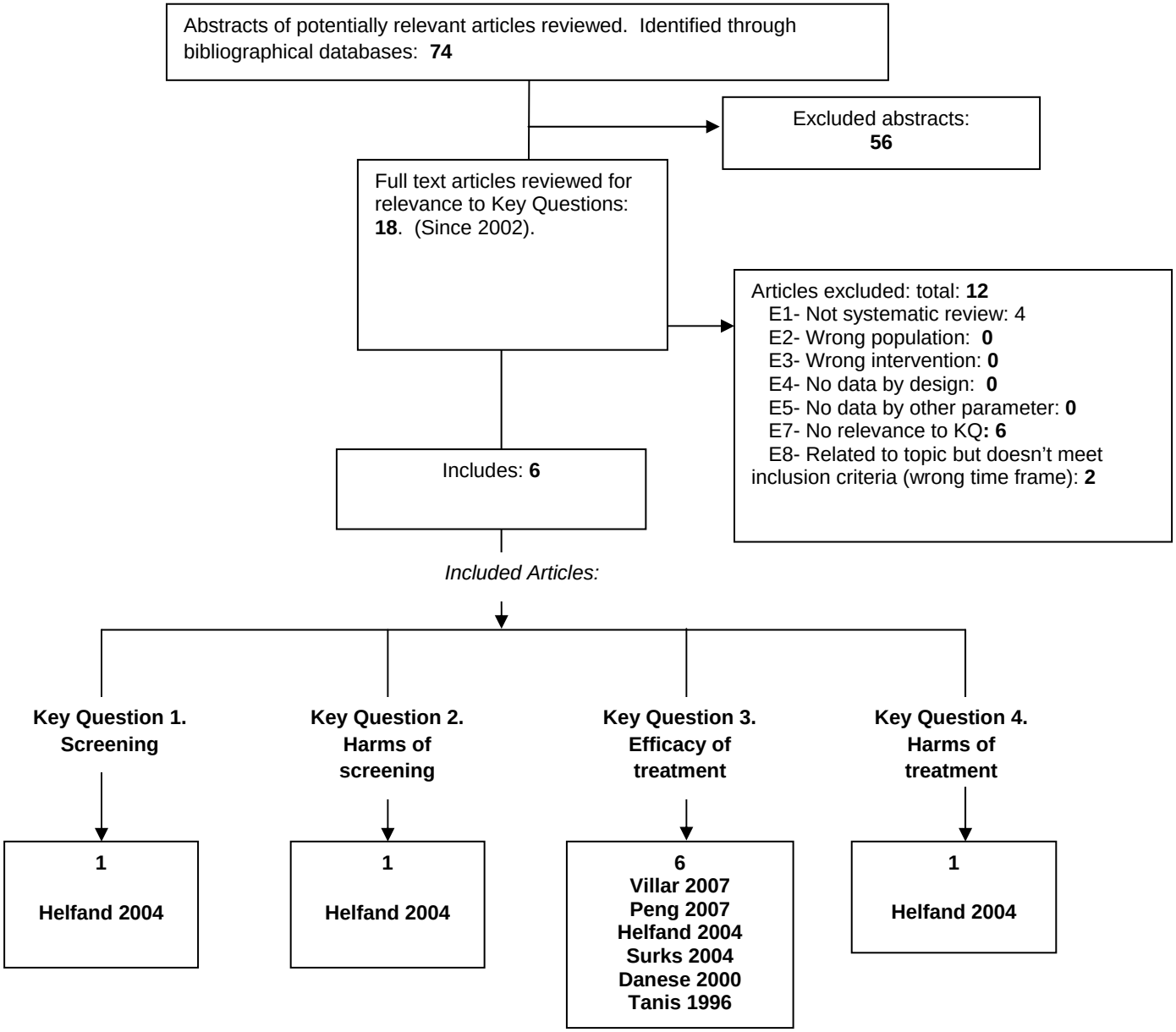
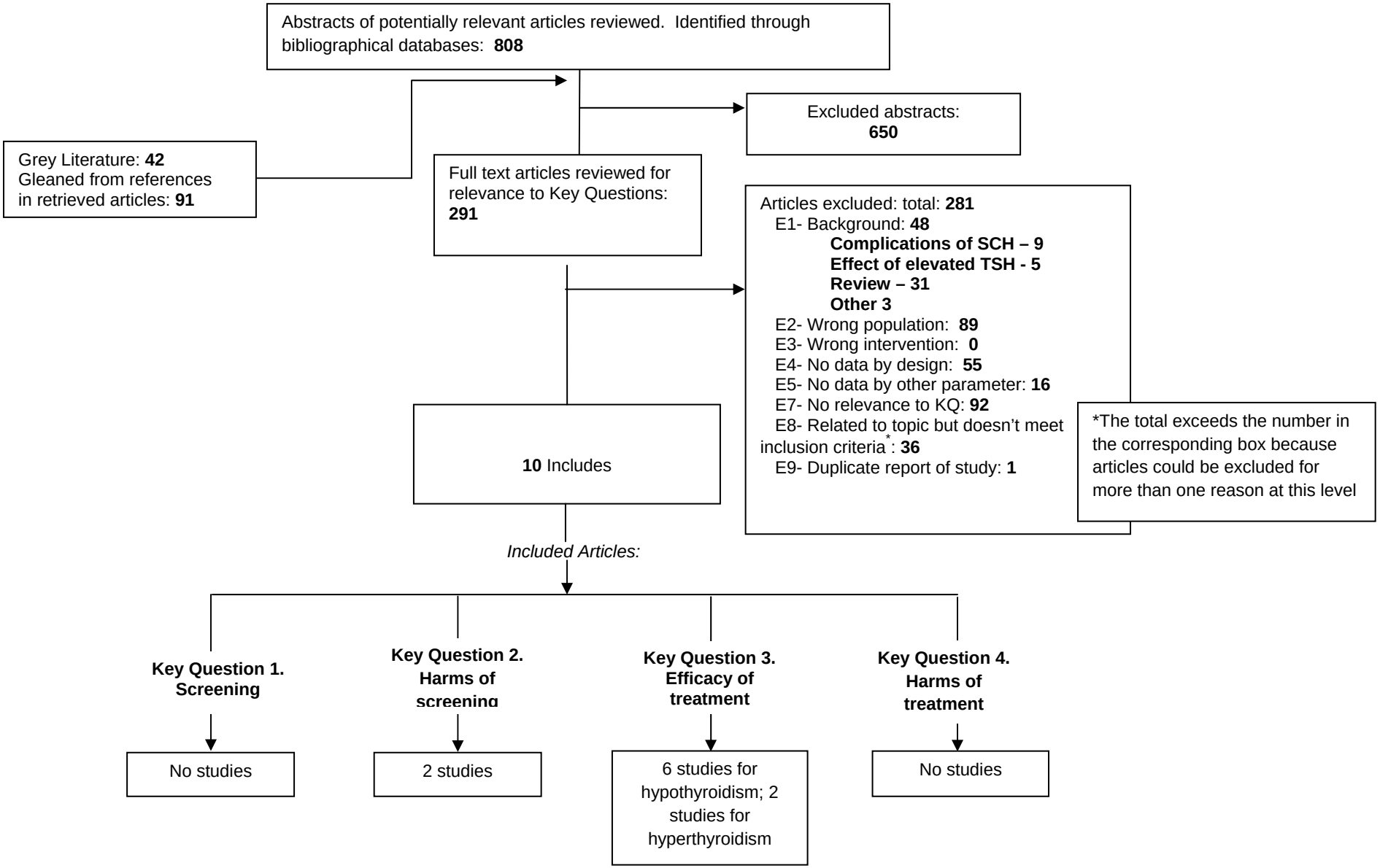


FIGURE B1B. Individual Study Literature flow diagram



*Uncompleted trials and studies that did not meet inclusion criteria for quality or study design.

FIGURE B1C. Foreign Language Literature flow diagram

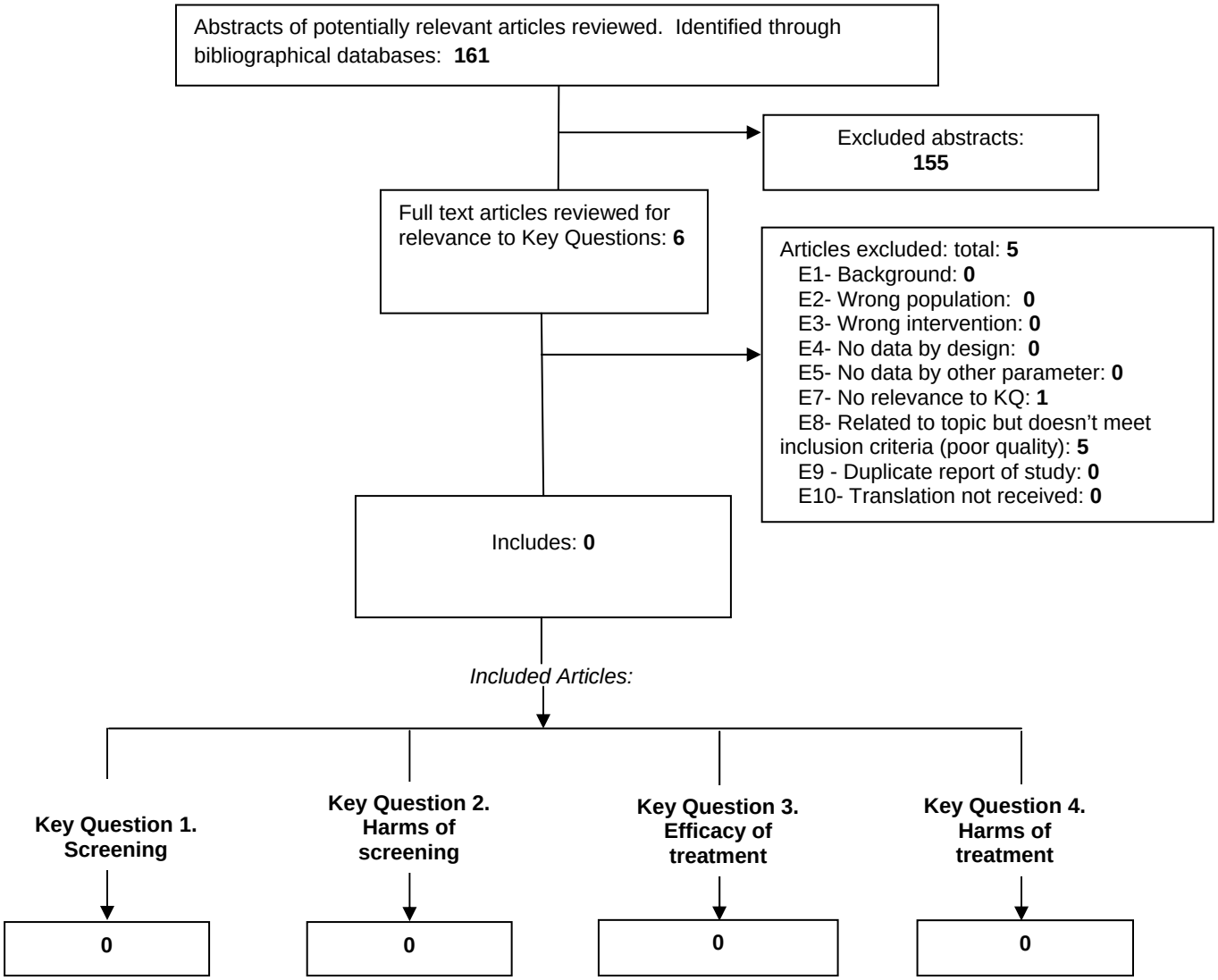


TABLE B1A. SEARCH STRATEGY for Systematic Reviews and Observational Studies

MEDLINE (PubMed) 3/3/10		
Set#	**Concept**	**Search strategy**
#1	Sub-clinical Thyroid Disease	(Hyperthyroidism [Mesh] OR Hypothyroidism [Mesh]OR (hypothyr* OR hypo-thyr* OR hyperthyr* OR hyper-thyr*) [tiab] OR (thyroid deficien* OR thyroid insufficien* OR thyroid failure) [tiab]) AND ((mild OR compens* OR subclinic* OR moderat* OR short-term) [tiab]) OR elevated tsh [tiab])
#2	Screening	Mass Screening [mesh]OR Thyroid Function Tests [mesh]OR (screening OR casefinding OR case finding) [tiab]
#3	Treatment for hyperthyroidism	anti-thyroid [tiab]OR methimazole [tiab]OR Methimazole [mesh]OR propylthiouracil [tiab]OR Propylthiouracil [mesh]OR (radioactive [tiab] OR radioiodine [tiab])
#4	Treatment for hypothyroidism	T3 [tiab] OR T4 [tiab] OR thyroxine [tiab] OR thyroxine [mesh] OR levothyroxine [tiab] OR triiodothyronine [tiab] OR triiodothyronine[mesh]OR liothyronine [tiab] OR (thyrolar [tiab] OR liotrix [tiab]) AND (therapeutic use [sh] OR treatment [tiab] OR therapy [tiab])
#5	Screening or treatment of sub-clinical thyroid disease	#1 AND (#2 OR #3 OR #4)
#6	Systematic reviews	systematic[sb]
#7	Observational Studies	((((((((cohort studies[MeSH Terms]) OR comparative study[MeSH Terms]) OR follow-up studies[MeSH Terms]) OR prospective studies[MeSH Terms]) OR risk factors[MeSH Terms]) OR cohort[Title/Abstract]) OR compared[Title/Abstract]) OR groups[Title/Abstract]) OR multivariate[Title/Abstract]
Systematic Reviews of screening or treatment for subclinical thyroid disease		#6 AND #5 N=39
Observational Studies of Screening for subclinical thyroid diesease		#1 AND #2 AND #7 limited to year 2002 and beyond N=236
[MeSH] = exploded term, all subterms and subtrees included [tiab] = in title and abstract * = truncation		

Cochrane Register Database of Systematic Reviews and Database of Abstracts of Reviews of Effects (OVID) 3/3/2010		
Set #	**Concept**	**Search Strategy**
#1	Sub-clinical Thyroid Disease	((hyperthyroidism.mp. OR hypothyroidism.mp. OR (hypothryr* or hypo-thyr* or hyperthryr* or hyper-thyr*).mp. OR (thyroid deficien* or thryroid insufficien* or thryroid failure).mp.) AND ((mild or compens* or subclinic* or moderat* or short-term).mp.)) OR elevated adj3 tsh.mp.
#2	Screening	mass screening.mp. or OR thyroid function tests.mp. or OR screening.mp. OR casefinding.mp OR case finding.mp.
#3	Treatment for hyperthyroidism	Antithyroid Agents.mp. OR anti-thyroid.mp. OR methimazole.mp. OR propylthiouracil.mp. OR radioiodine.mp. or radioactive.mp.
#4	Treatment for hypothyroidism	t3.mp. OR t4.mp. OR thyroxine.mp. OR levothyroxine.mp. OR triiodothyronine.mp. OR liothyronine.mp. OR thyrolar.mp. or liotrix.mp.
Systematic Reviews of screening or treatment for subclinical thyroid disease		#1 AND (#2 OR #3 OR #4) N=40 after deduplication 35

TABLE B1B. SEARCH STRATEGY FOR INDIVIDUAL STUDIES

MEDLINE (PubMed)		
Set#	**Concept**	**Search strategy**
#1	Sub-clinical Thyroid Disease	(Hyperthyroidism [mesh] OR Hypothyroidism [mesh](hypothyr* OR hypo-thyr* OR hyperthyr* OR hyper-thyr*) [tiab] OR (thyroid deficien* OR thyroid insufficien* OR thyroid failure) [tiab]) AND ((mild OR compens* OR subclinic* OR moderat* OR short-term) [tiab]) OR elevated tsh [tiab]
#2	Screening	Mass Screening [mesh]OR Thyroid Function Tests [mesh]OR (screening OR casefinding OR case finding) [tiab]
#3	Treatment for hyperthyroidism	anti-thyroid [tiab]OR methimazole [tiab]OR Methimazole [mesh]OR propylthiouracil [tiab]OR Propylthiouracil [mesh]OR (radioactive [tiab] OR radioiodine [tiab])
#4	Treatment for hypothyroidism	T3 [tiab] OR T4 [tiab] OR thyroxine [tiab] OR thyroxine [mesh] OR levothyroxine [tiab] OR triiodothyronine [tiab] OR triiodothyronine[mesh]OR liothyronine [tiab] OR (thyrolar [tiab] OR liotrix [tiab]) AND (therapeutic use [sh] OR treatment [tiab] OR therapy [tiab])
#5	Treatment in general	((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])
#6	Harms	(adverse effects [sh] OR poisoning [sh]OR toxicity [sh]OR contraindications [sh]OR complications [sh]) OR ((safe OR safety OR side-effect$ OR undesirable effect$ OR treatment emergent OR tolerability OR toxicity) [tw]) OR (adverse [tiab] AND (effect$ OR reaction$ OR event$ OR outcome$) [tiab])
#7	Patient issues of testing	Patient Satisfaction[Mesh]OR Perception[Mesh] OR Family[Mesh] OR Stress, Physiological[Mesh] OR Attitude to Health[Mesh]OR False Positive Reactions [Mesh] OR patient preference* [tiab] OR consequence* [tiab]OR cost [tiab] OR costs [tiab] OR false positive* [tiab]OR acceptability [tiab] OR worry [tiab]
#8	RCTs	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [MeSH] not (humans [MeSH] and animals [MeSH]))
KQ1 Screening for Subclinical Thyroid		#1 AND #2 AND #8

Disease	
KQ2 Harms of Screening	(#6 OR #7) AND (#1 AND #2)
KQ3a treatment hyper	#1 AND #3 AND #5
KQ3b treatment hypo	#1 AND #4 AND #8
KQ4 harms of treatment	(#3 OR #4) AND #6 AND #1

[MeSH] = exploded term, all subterms and subtrees included

[mesh: noexp] = non-exploded term, no subterms or subtrees included

[tiab] = in title and abstract

[tw] = word anywhere in the record

[pt] = publication type

* = truncation

all searches were limited to publication date 2002 or later

Cochrane Register of Controlled Trials (OVID)		
Set #	**Concept**	**Search Strategy**
#1	Sub-clinical Thyroid Disease	((hyperthyroidism.mp. or exp Hyperthyroidism/ OR exp Hypothyroidism/ or hypothyroidism.mp. OR (hypothryr* or hypo-thyr* or hyperthryr* or hyper-thyr*).mp. OR (thyroid deficien* or thryroid insufficien* or thryroid failure).mp.) AND ((mild or compens* or subclinic* or moderat* or short-term).mp.)) OR elevated adj3 tsh.mp.

#2	Screening	mass screening.mp. or exp Mass Screening/ OR thyroid function tests.mp. or exp Thyroid Function Tests/ OR screening.mp. OR casefinding.mp OR case finding.mp.
#3	Treatment for hyperthyroidism	exp Antithyroid Agents/ or anti-thyroid.mp. OR methimazole.mp. or exp Methimazole/ OR propylthiouracil.mp. or exp Propylthiouracil/ OR radioiodine.mp. or radioactive.mp.
#4	Treatment for hypothyroidism	t3.mp. OR t4.mp. OR exp Thyroxine/ or thyroxine.mp. OR levothyroxine.mp. OR exp Triiodothyronine/ or triiodothyronine.mp. OR liothyronine.mp. OR

		thyrolar.mp. or liotrix.mp.
KQ1/2 Screening		#1 AND #2
KQ3/4 Treatment		#2 AND (#3 OR #4)
all searches limited to publication date 2002 to current		

AGELINE (AARP.org)
hyperthyroidism ; hypothyroidism ; "thyroid deficien*" ; "thyroid insufficien*" ; "thyroid failure" AND “mild; compens* ; subclinic* ; moderat* ; “short-term”   [all content any position ; = OR]

EMBASE (EMBASE.com)	
Screening Search (KQ1 and KQ2)	(('hyperthyroidism'/syn OR 'hypothyroidism'/syn OR 'thyroid deficien' OR 'thyroid insufficien' OR 'thyroid failure') AND (mild OR compens* OR subclinic* OR moderat* OR 'short-term') OR 'elevated tsh') AND ('mass screening' OR 'thyroid function tests' OR screening OR casefinding OR case AND finding)
Treatment KQ3 and KQ4	((('hyperthyroidism'/syn OR 'hypothyroidism'/syn OR 'thyroid deficien' OR 'thyroid insufficien' OR 'thyroid failure') AND (mild OR compens* OR subclinic* OR moderat* OR 'short-term') OR 'elevated tsh') AND (('t3'/exp OR t4 OR 'thyroxine'/exp OR 'levothyroxine'/exp OR 'triiodothyronine'/exp OR 'liothyronine'/exp) AND ('therapeutic use' OR treatment OR 'therapy'/exp) OR ('anti thyroid' OR ('methimazole'/exp OR 'methimazole') OR propythiouracil)) AND (random OR ('placebo'/exp OR 'placebo') OR 'double blind')
Harms of Treatment KQ4	((('hyperthyroidism'/syn OR 'hypothyroidism'/syn OR 'thyroid deficien' OR 'thyroid insufficien' OR 'thyroid failure') AND (mild OR compens* OR subclinic* OR moderat* OR 'short-term') OR

	'elevated tsh') AND (('t3'/exp OR t4 OR 'thyroxine'/exp OR 'levothyroxine'/exp OR 'triiodothyronine'/exp OR 'liothyronine'/exp) AND ('therapeutic use' OR treatment OR 'therapy'/exp) OR ('anti thyroid' OR ('methimazole'/exp OR 'methimazole') OR propythiouracil)) AND (('adverse effects' OR ('poisoning'/exp OR 'poisoning') OR ('toxicity'/exp OR 'toxicity') OR contraindications OR complications OR safe OR ('safety'/exp OR 'safety') OR 'side effect'$ OR undesirable AND effect$ OR treatment AND emergent OR tolerability OR ('toxicity'/exp OR 'toxicity')) OR (adverse AND (effect$ OR reaction$ OR event$ OR outcome$)))

Grey Literature	
Type of information	**Sources Searched**
Clinical Trials	ClinicalTrials.gov Current Controlled Trials Clinical Study Results WHO Clinical Trials
Regulatory Information	FDA Health Canada Authorized Medicines for EU
Conference Proceedings	Conference Papers Index Scopus
Other	NIH RePORTER (a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions) HSRPROJ (a database providing access to ongoing grants and contracts in health

	services research) Hayes, Inc. Health Technology Assessment NY Academy of Medicine's Grey Literature Index

TABLE B1C. FOREIGN LANGUAGE SEARCH STRATEGY

CINAHL (EBSCO) 1-15-2010		
Set#	**Concept**	**Search strategy**
#1 S17 N=266	Sub-clinical Thyroid Disease	(((MH "Hyperthyroidism+") OR (MH "Hypothyroidism+") OR (ti hypothyr* OR ti hypo-thyr* OR ti hyperthyr* OR ti hyper-thyr* OR ab hypothyr* OR ab hypo-thyr* OR ab hyperthyr* OR ab hyper-thyr* OR ti thyroid deficien* OR ti thyroid insufficien* OR ti thyroid failure OR ti thyroid deficien* OR ti thyroid insufficien* OR ti thyroid failure)) AND (ti mild OR ti compens* OR ti subclinic* OR ti moderat* OR ti short-term OR ab mild OR ab compens* OR ab subclinic* OR ab moderat* OR ab short-term)) OR (ti elevated tsh OR ab elevated tsh)
#2 S22 N=53698	Screening	(MH "Health Screening+") OR (MH "Thyroid Function Tests+") OR (ti screening OR ti casefinding OR ti case finding) OR (ab screening OR ab casefinding OR ab case finding)
#3 S28 N=382	Treatment for hyperthyroidism	radioiodine OR ti radioactive OR ("anti-thyroid") or (MH "Thyroid Antagonists") OR propythiouracil OR methimazole
#4 S41 N=1082	Treatment for hypothyroidism	(liotrix OR thyrolar OR liothyronine OR triiodothyronine OR "levothyroxine" OR ("thyroxine") OR (MH "Thyroxine") OR ti t4 OR ab t4 OR ti T3 OR ab T3) AND (ti treatment OR ab treatment OR ti therapy OR ab therapy OR ("therapeutic use") or (MH "Therapeutics"))
#5 S48 N=647228	Treatment in general	(MH "Therapeutics+") OR (MH "Random Assignment") OR ti random* OR ab random* OR pt clinical trial OR (MH "Clinical Trials+") OR (ti clinical OR ab clinical) AND (ti trial OR ab trial)
#6 S55 N=372918	Harms	("adverse effects") OR (MH "Adverse Drug Event") OR (MH "Adverse Health Care Event") OR ("poisoning") or (MH "Poisoning") OR ("toxicity") or (MH "Drug Toxicity") OR "contraindications" OR ("complications") or (MH "Treatment Complications, Delayed") OR ("safety") OR (MH "Safety")
#7 S63 N=149782	Patient issues of testing	patient preference* OR consequence* OR cost OR costs OR false positive* OR acceptability OR worry OR (MH "False Positive Results") OR (MH "False Negative Results") OR (MH "Attitude to Health") OR (MH "Stress") OR (MH "Family") OR (MH "Perception") OR (MH "Patient Satisfaction")
#8 S68 N=80675	RCTs	(MH "Clinical Trials") OR ti randomized OR ti placebo OR ti randomly
KQ1 Screening for Subclinical Thyroid Disease		#1 AND #2 AND #8 (2 results both in English)
KQ2 Harms of Screening		(#6 OR #7) AND (#1 AND #2) (42 results, 2 non-English)

KQ3a treatment hyper	#1 AND #3 AND #5 (4 results all in English)
KQ3b treatment hypo	#1 AND #4 AND #8 (10 results, 1 non-English)
KQ4 harms of treatment	(#3 OR #4) AND #6 AND #1 (40 results, 2 non-English, one of these is duplicate)
	4 non-English articles found

1/15/2010

WHO Global Health Library (includes African Index Medicus, Index Medicus for the Eastern Mediterranean Region, Latin American and Caribbean Health Sciences Literature, Pan American Health Organization database, WHO Library Database, WHO Western Pacific Region database)

SEARCH: (Hyperthyrodism OR hypothyroidism) AND subclinical AND YEAR>= 2002 AND non-English language

TABLE B2. Criteria for Inclusion/Exclusion of Studies in the Review

- KQ 1a and 1b: RCT
- KQ 2: RCT, controlled trials, cohort studies, case-control studies, and observational databases.
- KQ 3: RCT, controlled trials, cohort studies, and case-control studies.
- KQ 4: RCT, controlled trials, cohort studies, case-control studies and observational databases.

Costs: A discussion of the costs or cost-effectiveness of screening is not within the scope of this review.

Target Population: Community living adults, without history of thyroid disease or symptoms of overt hypothyroidism or hyperthyroidism, representative of primary care settings. Hospitalized or recently hospitalized participants are to be excluded as these individuals may have elevated TSH levels.

Date Range: Publications from 2002 to the present will be included in the study. This start date was chosen to provide a small period of overlap with the publication date range used in the prior 2004 review.

Non-English language studies will be considered for inclusion in the review, and a search for relevant grey literature will be conducted.

TABLE B3. Criteria for Assessing Internal Validity of Individual Studies

The Methods Work Group for the US Preventive Services Task Force (USPSTF) developed a set of criteria by which the internal validity of individual studies could be evaluated. The USPSTF accepted the criteria, and the associated definitions of quality categories, that relate to internal validity at its September 1999 meeting.

This appendix describes the criteria relating to internal validity and the procedures that topic teams follow for all updates and new assessments in making these judgments.

All topic teams use initial "filters" to select studies for review that deal most directly with the question at issue and that are applicable to the population at issue. Thus, studies of any design that use outdated technology or that use technology that is not feasible for primary care practice may be filtered out before the abstraction stage, depending on the topic and the decisions of the topic team. The teams justify such exclusion decisions if there could be reasonable disagreement about this step. The criteria below are meant for those studies that pass this initial filter.

Presented below are a set of minimal criteria for each study design and then a general definition of three categories: "good," "fair," and "poor," based on those criteria. These specifications are not meant to be rigid rules but rather are intended to be general guidelines, and individual exceptions, when explicitly explained and justified, can be made. In general, a "good" study is one that meets all criteria well. A "fair" study is one that does not meet (or it is not clear that it meets) at least one criterion but has no known "fatal flaw." "Poor" studies have at least one fatal flaw.

a. Systematic Reviews

Criteria:

- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance are especially important for systematic reviews

Definition of ratings from above criteria:

Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

Case-Control Studies

Criteria:

- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Definition of ratings based on criteria above:

Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate equal to or greater than 80 percent; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables.

Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rate less than 80 percent or attention to some but not all important confounding variables.

Poor: Major selection or diagnostic work-up biases, response rates less than 50 percent, or inattention to confounding variables.

ii. Randomized Controlled Trials and Cohort Studies

Criteria:

- Initial assembly of comparable groups
  - for RCTs: adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - for cohort studies: consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs.

Definition of ratings based on above criteria:

Good: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80 percent); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.

Fair: Studies will be graded “fair” if any or all of the following problems occur, without the fatal flaws noted in the “poor” category below: Generally comparable groups are assembled initially but some question remains whether some (although not

major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.

Poor: Studies will be graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

a. Diagnostic Accuracy Studies

Criteria:

- Screening test relevant, available for primary care, adequately described
- Study uses a credible reference standard, performed regardless of test results
- Reference standard interpreted independently of screening test
- Handles indeterminate results in a reasonable manner
- Spectrum of patients included in study
- Sample size
- Administration of reliable screening test

Definition of ratings based on above criteria:

Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (more than 100) broad-spectrum patients with and without disease.

Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independent of screening test; moderate sample size (50 to 100 subjects) and a "medium" spectrum of patients.

Poor: Has fatal flaw such as: Uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size or very narrow selected spectrum of patients.

Appendix C

Evidence Tables and Excluded Studies

TABLE C1. INCLUDED SYSTEMATIC REVIEWS

Author Year; n studies	Study types, n	Total participants	SR assessment of quality of primary literature	Overlapping studies n*†	Quality of SR	Comments
Helfand 2004; 8	RCT, 8; Metanalyses of observational studies, 2	RCT, 291+	Screening Benefits: N/A Screening Harms: Poor Yield: Good Treatment Benefits: Poor Treatment Harms Osteoporosis: Good Overtreatment: Good Other: Poor	Danese: 2 Villar: 6	Good AMSTAR 9/11	
Villar 2007; 12	RCT, 12	RCT, 461+	Maximum Jadad score of 5; median score of 12 studies was 4 with a range of 3 to 5	Danese: 2 Helfand: 6	Good AMSTAR 10/11	Assessed the quality of the individual studies using the Jadad and Schulz criteria, but did not assess the overall strength of the evidence of the body of literature

+ One study did not report n

* 2 studies (Cooper 1984; Jaeschke 1996) were common to all three reviews

† See Table N Study Concordance for details

TABLE C2. TREATMENT EVIDENCE TABLE (SUBCLINICAL HYPOTHYROIDISM)

Author, year Duration	Country and population	Study design	Sample size Begun/Completed	Results[a]		Quality Score
1. Caraccio, 2005 6 months	Italy. Patients recruited from outpatient clinic. All suffered from Hashimoto's thyroiditis and had positive antibodies TSH > 3.6 mIU/L	Randomized, placebo-controlled trial. Randomization method not stated. Allocation concealment not described.	LT4: 12/12 Placebo: 11/11	BMI	⇔	**Fair**
2. Iqbal, 2006 12 months	Norway. SCH patients found from general health survey. 3.5 < TSH < 10 mIU/L	Randomized placebo-controlled trial. Randomization method not stated. Blinding and allocation concealment not described.	LT4: 32/? Placebo: 32/?	Total Cholesterol LDL HDL Triglycerides BMI	⇔ ⇔ ⇔ ⇔ ⇔	**Fair**
3. Jorde, 2006 12 months	Norway. SCH patients found from general health survey. 3.5 < TSH < 10 mIU/L	Randomized placebo-controlled trial. Randomization method not stated. Allocation concealment not described.	LT4: 36/36 Placebo: 33/32	Cognitive General Health Depression	⇔ ⇔ ⇔	**Fair**

4. Mikhail, 2008 52 weeks	Kuwait. Patients, age 15-60, from endocrinology outpatient clinic. 4 < TSH < 10 mIU/L	Double-blind, Placebo-controlled trial. Blinding stated but not described; allocation concealment not stated.	LT4: 60/? Placebo: 60/?	Total Cholesterol LDL HDL Triglycerides	⇧ $p < 0.03$ ⇧ $p < 0.001$ ⇔ ⇔	**Fair**
5. Nagasaki, 2009 5 months	Japan. Newly diagnosed patients with SCH due to chronic thyroiditis with positive antibodies TSH “above the normal upper limit”	Randomized, placebo-controlled study. Randomization method not described. Blinding of patients but not caretakers or assessors described. Allocation concealment not described.	LT4: 48/? Placebo: 47/?	Total Cholesterol LDL HDL Triglycerides Blood Pressure BMI	⇔ ⇔ ⇔ ⇔ ⇔ ⇔	**Fair**

6. Razvi, 2007 24 weeks	United Kingdom. Patients from urban, general practice settings identified through laboratory database, not through screening. TSH > 4 mIU/L	Randomized, placebo-controlled cross-over (12-week) trial	LT4:50/50 Placebo: 50/49	Total Cholesterol LDL HDL Triglycerides Blood pressure Weight QoL	⇧ $p < 0.001$ ⇧ $p < 0.001$ ⇔ ⇔ ⇔ ⇔ ⇔	**Good**

[a] For details see separate results tables by outcome – Tables 6a-6g

⇔: No evidence of benefit

⇧: Evidence of benefit

TABLE C3. QUALITY OF LIFE

Jorde, 2006 (Norway)	**Thyroxine**	**N**	**Placebo**	**N**
Dosage	109.7 mcg/day (avg)			
Cognitive Before	1.8 +/- 3.4	34	-1.1 +/- 4.7	31
Cognitive After	1.5 +/- 3.7	35	-0.9 +/- 4.8	30
Difference	n.s.		n.s.	
GHQ-30 Before	1.5 +/- 2.3	36	0.7 +/- 1.3	33
GHQ-30 After	1.9 +/- 3.3	36	1.2 +/- 2.0	32
Difference	n.s.		n.s.	
BDI Before	4.4 +/- 3.7	36	3.7 +/- 3.8	33
BDI After	4.3 +/- 3.6	36	3.3 +/- 4.0	33
Difference	n.s.		n.s.	

Razvi, 2007 (UK)					**Delta Mean Difference**	**P**
	Thyroxine	**N**	**Placebo**	**N**		
Dosage	100 mcg/day for 12 weeks					
T-QoL After	-1.1 +/- 1	50	-1.2 +/- 0.9	50	0.2 (0.02 to 0.36)	n.s.
Sex life After	-2.3 +/- 2.7	50	-2.7 +/- 2.8	50	0.3 (0.02 to 0.7)	n.s.
Motivation After	-3.6 +/- 2.7	50	-3.7 +/- 2.7	50	0.4 (-0.4 to 0.9)	n.s.
Worries After	-2.5 +/- 3	50	-2.8 +/- 2.9	50	0.2 (-0.2 to 0.7)	n.s.
AWI* After	-2.7 +/- 2.4	50	-2.8 +/- 2.3	50	0.1 (-0.3 to 0.5)	n.s.

*AWI: Average weighted impact of all 18 domains

TABLE C4. WEIGHT (kg)/BMI (kg/m^2) (SUBCLINICAL HYPOTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Change Difference	P
Caraccio, 2005 (Italy)		BMI	BMI				
Thyroxine	65 mcg (avg) for 6 months	22.8 +/- 0.9	22.3 +/- 0.9	-0.5	n.s.		
Placebo		22.6 +/- 0.6	22.7 +/- 0.6	0.1	n.s.		
						-0.6†	n.s.
Quality: Fair							
Iqbal, 2006 (Norway)		BMI	BMI				
Thyroxine	50 mcg/day 1st 6 weeks 100 mcg/day final 46 weeks	28.7 +/- 5.7	28.4 +/- 5.8	-0.3	n.s.		
Placebo		27.1 +/- 3.7	27.0 +/- 4.1	-0.1	n.s.		
						-0.2†	n.s.
Quality: Fair							
Nagasaki, 2009 (Japan)		BMI	BMI				
Thyroxine	Not stated for 5 months	22.0 +/- 0.48	21.8 +/- 0.48	-0.2	n.s.		
Placebo		22.2 +/- 0.51	22.1 +/- 0.50	-0.1	n.s.		
						-0.1†	n.s.
Quality: Fair							
Razvi, 2007 (UK)		WEIGHT	WEIGHT				
Thyroxine	100 mcg/day for 12 weeks	75.9 +/- 15.9	75.8 +/- 16.5	-0.1	n.s.		
Placebo		77.0 +/- 16.9	76.5 +/- 16.7	-0.5	n.s.		
						-0.6 (-1.1 to -0.1)	n.s.
Quality: Good							

†Difference calculated from numbers provided

TABLE C5. BLOOD PRESSURE (mmHg) (SUBCLINICAL HYPOTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Change Difference	P
Nagasaki, 2009 (Japan)		Systolic	Systolic				
Thyroxine	Not stated for 5 months	132.8 +/- 3.9	128.8 +/- 3.8	-4.0	n.s.		
Placebo		133.1 +/- 3.4	132.2 +/- 3.5	-0.9	n.s.		
						-3.1†	n.s.
		Diastolic	Diastolic				
Thyroxine		74.3 +/- 2.9	72.7 +/- 2.2	-1.6	n.s.		
Placebo		75.7 +/- 1.9	72.8 +/- 2.0	-2.9	n.s.		
						1.3†	n.s.
Quality: Fair							
Razvi, 2007 (UK)		Systolic	Systolic				
Thyroxine	100 mcg/day for 12 weeks	135.7 +/- 22.6	132.8 +/- 22.8	-2.9	n.s.		
Placebo		129.4 +/- 20.1	134.6 +/- 22.9	5.2	n.s.		
						-1.8 (-4.6 to 1.0)	n.s.
		Diastolic	Diastolic				
Thyroxine		80.8 +/- 8.3	78.8 +/- 10.3	-2.0	n.s.		
Placebo		79.1 +/- 10.0	79.9 +/- 9.6	0.8	n.s.		
						-1.1 (-2.8 to 0.5)	n.s.
Quality: Good							

†Difference calculated from numbers provided

TABLE C6. TOTAL CHOLESTEROL (mg/dL)* (SUBCLINICAL HYPOTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Change Difference	p
Iqbal, 2006 (Norway)							
Thyroxine	50 mcg/day 1st 6 weeks 100 mcg/day final 46 weeks	227.7 +/- 42.5	220.0 +/- 42.5	-7.7	n.s.		
Placebo		223.9 +/- 30.9	223.9 +/- 34.7	0	n.s.		
						-7.7†	n.s.
Quality: Fair							
Mikhail, 2008 (Kuwait)							
Thyroxine	72+/-3.8 mcg/day (avg) for 52 weeks	194.9 +/- 37.8	183.0 +/0 33.6	-11.9	< 0.001		
Placebo		192.6 +/- 27.8	194.5 +/- 25.9	1.9	n.s.		
						-13.8†	0.03
Quality: Fair							
Nagasaki, 2009 (Japan)							
Thyroxine	Not stated for 5 months	215.8 +/- 10.4	200.3 +/- 6.2	-15.5	n.s.		
Placebo		213.5 +/- 9.7	205.7 +/- 9.3	-7.8	n.s.		
						-7.7†	n.s.
Quality: Fair							
Razvi, 2007 (UK)							
Thyroxine	100 mcg/day for 12 weeks	235.5 +/- 34.7	220.0 +/- 38.6	-15.5			
Placebo		231.6 +/- 54.0	231.6 +/- 38.6	0		-13.5 (-19.3 to -7.72)	< 0.001
Quality: Good							

*Converted from mmol/liter by multiplying by 38.6

†Difference calculated from numbers provided

TABLE C7. LDL (mg/dL)* (SUBCLINICAL HYPOTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Change Difference	p
Iqbal, 2006 (Norway)							
Thyroxine	50 mcg/day 1st 6 weeks 100 mcg/day final 46 weeks	142.8 +/- 34.7	139.0 +/- 34.7	-3.8	n.s.		
Placebo		139.0 +/0 30.9	139.0 +/0 38.6	0	n.s.		
						-3.8†	n.s.
Quality: Fair							
Mikhail, 2008 (Kuwait)							
Thyroxine	72+/-3.8 mcg/day (avg) for 52 weeks	127.4 +/- 34.7	111.6 +/- 22.8	-15.8	< 0.01		
Placebo		107.7 +/- 23.2	120.0 +/- 29.7	+12.3	< 0.001		
						-28.1†	< 0.001
Quality: Fair							
Nagasaki, 2009 (Japan)							
Thyroxine	Not stated for 5 months	138.2 +/- 8.5	121.2 +/- 11.2	-17.0	n.s.		
Placebo		137.4 +/- 7.7	129.7 +/- 7.3	-7.7	n.s.		
						-9.3†	
Quality: Fair							
Razvi, 2007 (UK)							
Thyroxine	100 mcg/day for 12 weeks	139.0 +/- 30.9	131.2 +/- 30.9	-7.8			
Placebo		139.0 +/- 46.3	142.8 +/- 34.7	+3.8			
						-7.7 (-15 to -3.9)	<0.001
Quality: Good							

*Converted from mmol/liter by multiplying by 38.6

†Difference calculated from numbers provided

TABLE C8. HDL (mg/dL)* (SUBCLINICAL HYPOTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Change Difference	P
Iqbal, 2006 (Norway)							
Thyroxine	50 mcg/day 1st 6 weeks 100 mcg/day final 46 weeks	57.9 +/- 15.4	57.9 +/- 15.4	0.0	n.s		
Placebo		57.9 +/- 23.2	57.9 +/- 19.3	0.0	n.s.	0†	n.s.
Quality: Fair							
Mikhail, 2008 (Kuwait)							
Thyroxine	72+/-3.8 mcg/day (avg) for 52 weeks	46.3 +/- 12.7	45.9 +/- 12.4	-0.4	n.s.		
Placebo		44.4 +/- 8.9	42.5 +/- 9.7	-1.9	n.s.		
						1.5†	n.s.
Quality: Fair							
Nagasaki, 2009 (Japan)							
Thyroxine	Not stated for 5 months	54.4 +/- 1.9	54.4 +/- 3.1	0.0	n.s.		
Placebo		53.3 +/- 2.3	53.7 +/- 2.3	0.4	n.s.	-0.4†	n.s.
Quality: Fair							
Razvi, 2007 (UK)							
Thyroxine	100 mcg/day for 12 weeks	65.6 +/- 19.3	61.8 +/- 19.3	-3.8			
Placebo		61.8 +/- 15.4	65.6 +/- 19.3	3.8			
						-2.3 (-3.9 to -0.4)	n.s.
Quality: Good							

*Converted from mmol/liter by multiplying by 38.6

†Difference calculated from numbers provided

TABLE C9. TRIGLYCERIDES (mg/dL)* (SUBCLINICAL HYPOTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Change Difference	P
Iqbal, 2006 (Norway)							
Thyroxine	50 mcg/day 1st 6 weeks 100 mcg/day final 46 weeks	132.9 +/- 79.7	132.9 +/- 88.6	0	n.s.		
Placebo		141.8 +/- 79.7	141.8 +/- 62.0	0	n.s.		
						0†	n.s.
Quality: Fair							
Mikhail, 2008 (Kuwait)							
Thyroxine	72+/-3.8 mcg/day (avg) for 52 weeks	104.5 +/- 62.9	84.2 +/- 47.0	-20.3	< 0.002		
Placebo		89.5 +/- 58.5	93.9 +/- 52.3	4.4	n.s.		
						-24.7†	n.s.
Quality: Fair							
Nagasaki, 2009 (Japan)							
Thyroxine	Not stated for 5 months	118.7 +/- 12.4	132.9 +/- 14.2	14.2	n.s.		
Placebo		121.4 +/- 11.5	122.3 +/- 12.4	.9	n.s.		
						13.3†	n.s.
Quality: Fair							
Razvi, 2007 (UK)							
Thyroxine	100 mcg/day for 12 weeks	106.3 (62.0 to 327.8)	115.2 (44.3 to 363.3)	8.9	n.s.		
Placebo		106.3 (44.3 to 274.7)	115.2 (35.4 to 451.9)	8.9	n.s.		
						-5.3 (-17.7 to -8.9)	n.s.
Quality: Good							

*Converted from mmol/liter by multiplying by 88.6

†Difference calculated from numbers provided

TABLE C10. TREATMENT EVIDENCE TABLE (SUBCLINICAL HYPERTHYROIDISM)

Author, year Duration	Country and population	Study design	Sample size Begun/Completed	Results[a]		Quality Score
1. Buscemi, 2007 12 months	Italy. Newly diagnosed patients. TSH < 0.49 mIU/L	Controlled trial. Treatment allocation through alternate assignment. Patients given option of changing assigned group (none did). Not blinded.	Methimazole: 7/7 No treatment: 7/7	BMI Blood Pressure	⇧ ⇔	**Poor**
2. Yonem, 2002 6 months	Turkey. Patients with SCH for 6 – 60 months. 2 patients with Graves disease and 8 with autonomous nodule. TSH < 0.4 mIU/L	Randomized controlled trial. Randomization method not stated. Not blinded. Allocation concealment not described. Multiple treatments not analyzed separately	Propylthiouracil: 9/? Radioactive Iodine: 1/? No Treatment: 10/? Treatments not analyzed separately	Total Cholesterol LDL HDL Triglycerides Bone Mineral Density Blood Pressure	⇔ ⇔ ⇔ ⇔ ⇔ ⇧	**Poor**

[a] For details see separate results tables by outcome – Tables 7a-7d

⇔: No evidence of benefit

⇧: Evidence of benefit

TABLE C11. BMI (kg/m^2) (SUBCLINICAL HYPERTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Before-After Difference†	P
Buscemi, 2007 (Italy)							
Methimazole	TSH > 0.01: 10 mg/day TSH <= 0.01: 15 mg/day for 12 months	27.3 +/- 1.3	27.8 +/- 1.4	0.5	<0.05		
No Treatment		27.9 +/- 1.2	28.1 +/- 1.0	0.2	n.s.		
						0.3	?
Quality: Poor							

†Difference calculated from numbers provided

TABLE C12. BLOOD PRESSURE (mmHg) (SUBCLINICAL HYPERTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Before-After Difference†	P
Buscemi, 2007 (Italy)		Systolic	Systolic				
Methimazole	TSH > 0.01: 10 mg/day TSH <= 0.01: 15 mg/day for 12 months	139 +/- 6	136 +/- 4	-3	n.s.		
No Treatment		136 +/- 8	126 +/- 11	-10	n.s.		
						7	n.s.
		Diastolic	Diastolic				
Methimazole		79 +/- 3	78 +/- 3	-1	n.s.		
No Treatment		78 +/- 3	80 +/- 3	+2	n.s.		
						-3	n.s.
Quality: Poor							
Yonem, 2002 (Turkey)		Daytime Systolic	Daytime Systolic				
Propylthiouracil or Radioactive Iodine	Propylthiouracil 150 mg/day Radioactive Iodine not stated for 6 months	115.00 +/- 2.78	112.42 +/- 2.66	-2.58	<0.05		
No Treatment		114.50 +/- 3.21	113.70 +/- 2.62	-0.80	n.s.		
						-1.78	?
		Daytime Diastolic	Daytime Diastolic				
Propylthiouracil or Radioactive Iodine		71.10 +/- 2.37	69.40 +/- 1.78	-1.70	n.s.		
No Treatment		72.70 +/- 2.00	72.10 +/- 2.37	-0.60	n.s.		
						-1.1	
		Nighttime Systolic	Nighttime Systolic				
Propylthiouracil or Radioactive Iodine		98.50 +/- 2.96	100.10 +/- 2.25	1.60	n.s.		
No Treatment		100.60 +/- 2.29	101.60 +/- 1.96	1.00	n.s.		
						0.6	n.s.
		Nighttime Diastolic	Nighttime Diastolic				
Propylthiouracil or Radioactive Iodine		62.80 +/- 1.95	61.50 +/- 1.40	-1.30	n.s.		
No Treatment		62.30 +/- 1.71	61.80 +/- 2.80	-0.50	n.s.		
						-0.8	n.s.
Quality: Poor							

†Difference calculated from numbers provided

TABLE C13. BONE MINERAL DENSITY (g/cm^2) (SUBCLINICAL HYPERTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Before-After Difference†	P
Yonem, 2002 (Turkey)		Femur Neck	Femur Neck				
Propylthiouracil or Radioactive Iodine	Propylthiouracil 150 mg/day Radioactive Iodine not stated for 6 months	0.828 +/- 0.038	0.826 +/- 0.042	-0.002	n.s.		
No Treatment		0.848 +/- 0.017	0.868 +/- 0.019	0.020	n.s.		
						-0.022	n.s.
		Lumbar Vertebra	Lumbar Vertebra				
Propylthiouracil or Radioactive Iodine		0.991 +/- 0.046	0.998 +/- 0.048	0.007	n.s.		
No Treatment		0.968 +/- 0.030	0.968 +/- 0.030	0.000	n.s.		
Quality: Poor						.007	n.s.

†Difference calculated from numbers provided

TABLE C14. LIPIDS (mg/dL) (SUBCLINICAL HYPERTHYROIDISM)

Study, Year (Country)	Dosage	Before	After	Before-After Difference†	p	Treatment/No Treatment Before-After Difference†	P
Yonem, 2002 (Turkey)		TOTAL CHOLESTEROL	TOTAL CHOLESTEROL				
Propylthiouracil or Radioactive Iodine	Propylthiouracil 150 mg/day Radioactive Iodine not stated for 6 months	183.0 +/- 12.0	182.6 +/- 8.9	-0.4	n.s.		
No Treatment		161.7 +/- 10.0	157.1 +/- 6.6	-4.6	n.s.		
						4.2	n.s.
		LDL	LDL				
Propylthiouracil or Radioactive Iodine		110.0 +/- 8.8	105.8 +/- 6.6	-4.2	n.s.		
No Treatment		86.9 +/- 6.9	91.1 +/- 5.8	4.2	n.s.		
						-8.4	n.s.
		HDL	HDL				
Propylthiouracil or Radioactive Iodine		54.4 +/- 4.6	47.5 +/- 3.9	-6.9	n.s.		
No Treatment		52.5 +/- 5.8	48.3 +/- 3.5	-4.2	n.s.		
						-2.7	n.s.
		TRIGLYCERIDES	TRIGLYCERIDES				
Propylthiouracil or Radioactive Iodine		124.0 +/- 15.9	39.9 +/- 23.9	-84.1	?		
No Treatment		93.9 +/- 10.6	76.2 +/- 14.2	-17.7	n.s.		
Quality: Poor						-66.4	n.s.

*Converted total cholesterol, LDL, and HDL from mmol/liter by multiplying by 38.6 and triglycerides by 88.6

†Difference calculated from numbers provided

Table C15. Excluded systematic reviews

1. Baskin HJ, Cobin RH, Duick DS, Gharib H, Guttler RB, Kaplan MM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2002;8(6):457. **Not a systematic review**

2. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of Subclinical Thyroid Dysfunction on the Heart. Annals of Internal Medicine. 2002 Dec 3;137(11):904. **Not a systematic review**

3. Bjorndal MM, Sandmo WK, Lu T, Jorde R. Prevalence and causes of undiagnosed hyperthyroidismin an adult healthy population. The Troms\o study. Journal of endocrinological investigation. 2008;31(10):856. **Not a systematic review.**

4. Danese MD, Ladenson PW, Meinert CL, Powe NR. Clinical review 115: effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. J. Clin. Endocrinol. Metab. 2000 Sep;85(9):2993-3001. **Fair quality review, Not in time frame for reviews.**

5. Faber J, Galloe AM. Changes in bone mass during prolonged subclinical hyperthyroidism due to L-thyroxine treatment: a meta-analysis. European Journal of Endocrinology. 1994;130(4):350. **Not in time frame for reviews**

6. Lindstedt G, Eliasson M. Bristande st\öd f\ör screening och terapi vid subklinisk tyreoideafunktionsrubbning. Lakartidningen. 2005;102(1-2):30-33. **Not a systematic review**

7. Nygaard B. Hyperthyroidism (primary). BMJ Clinical Evidence. 2008;3. **Not related to key questions (reviews treatment for hyperthyroidism.)**

8. Ochs N, Auer R, Bauer DC, Nanchen D, Gussekloo J, Cornuz J, et al. Meta-analysis: Subclinical Thyroid Dysfunction and the Risk for Coronary Heart Disease and Mortality. Annals of Internal Medicine. 2008 Jun 3;148(11):832-845. **Not related to key questions, but relevant for background.**

9. Palmieri EA, Fazio S, Lombardi G, Biondi B. Subclinical hypothyroidism and cardiovascular risk: a reason to treat? Treatments in Endocrinology. 2004;3(4):233–244. **Not a systematic review**

10. Peng L, Gu M. Influence of thyroxine treatment on serum lipid levels in patients with subclinical hypothyroidism: A meta-analysis. Academic Journal of the Second Military Medical University. 2007;28(5):519-523. **Poor quality review.**

11. Pham CB, Shaughnessy AF. Should we treat subclinical hypothyroidism? British Medical Journal. 2008;337(jul16 3):a834. **Not a systematic review**

12. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical Thyroid Disease: Scientific Review and Guidelines for Diagnosis and Management. JAMA. 2004 Jan 14;291(2):228-238. **Poor quality review**

13. Tanis BC, Westendorp GJ, Smelt HM. Effect of thyroid substitution on hypercholesterolaemia in patients with subclinical hypothyroidism: a reanalysis of intervention studies. Clin. Endocrinol. (Oxf). 1996 Jun;44(6):643-649. **Poor quality review, Not in time frame for reviews.**

14. Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, Perret GY. Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis. Journal of Clinical Endocrinology & Metabolism. 1996;81(12):4278. **Not in time frame for reviews**

15. Joffe RT, Brimacombe M, Levitt AJ, Stagnaro-Green A. Treatment of clinical hypothyroidism with thyroxine and triiodothyronine: a literature review and metaanalysis. Psychosomatics. 2007 48(5) 379-384. **Not related to key questions {Joffe, 2007 #11}**

Table C16. Excluded studies

1. 1R01AG032317-01A1, *Subclinical thyroid dysfunction in the elderly*. **No data by design**

2. 1R01MH080295-01A2, *Subclinical Hypothyroidism: Mood, Cognition and the effect of L-thyroxine treatment*. **No data by design**

3. 5R01HL076645-03, *Subclinical Thyroid Dysfunction & Risk of MI and Stroke*. **No relevance to key questions**

4. 5R21DK062787-02, *Neurocognitive effects of subclinical thyroid disease*. **Related to topic but does not meet inclusion criteria**

5. Abalovich, M., et al., *Subclinical hypothyroidism and thyroid autoimmunity in women with infertility*, in *Gynecol Endocrinol*. 2007. p. 279-83. **No relevance to key questions; Wrong population**

6. Abbott Laboratories. **No data by other parameter**

7. Abdelrazek, S.S., et al., *The Outcome of Radioiodine Therapy in Patient with Subclinical Hyperthyroidism*, in *19th Annual Congress of the European Association of Nuclear Medicine (EANM 06), Megaron International Conference Center, Athens (Greece), 30 Sep-4 Oct 2006*. 2006. p. P534 (333). **Related to topic but does not meet inclusion criteria**

8. Abdelrazek, S.S., et al., *The Effect of Radioiodine Therapy on Some Parameters of Oxidant/Antioxidant Balance in Patients with Subclinical Hyperthyroidism*, in *20th Annual Congress of the European Association of Nuclear Medicine (EANM 2007), Copenhagen Congress Center, Copenhagen (Denmark), 13-17 Oct 2007*. 2007. p. P445 (S353). **Related to topic but does not meet inclusion criteria**

9. Abdullatif, H.D. and A.P. Ashraf, *Reversible subclinical hypothyroidism in the presence of adrenal insufficiency*, in *Endocr Pract*. 2006. p. 572. **Wrong population**

10. Adrees, M., et al., *Effects of 18 months of L-T4 replacement in women with subclinical hypothyroidism*, in *Clin Endocrinol*. 2009. p. 298-303. **Related to topic but does not meet inclusion criteria**

11. Akinci, B., et al., *The alteration of serum soluble CD40 ligand levels in overt and subclinical hypothyroidism*, in *Hormones (Athens)*. 2007. p. 327-33. **Related to topic but does not meet inclusion criteria**

12. Al Sayed, A., et al., *Subclinical hypothyroidism is associated with early insulin resistance in Kuwaiti women*, in *Endocr J*. 2006. p. 653-7. **No data by other parameter; No relevance to key questions**

13. Alberiche, M., et al., *Thyrotropin levels and their relationship with cardiovascular risk factors in the island of Gran Canaria, Spain. Implications of lowering the upper reference limit of thyrotropin stimulating hormone*, in *J Endocrinol Invest*. 2009. p. 102-6. **Background – Complications of SCH**

14. Algun, E., et al., *Urinary beta-2 microglobulin in renal dysfunction associated with hypothyroidism*, in *Int J Clin Pract*. 2004. p. 240-3. **Wrong population**

15. Alzoubi, K.H., et al., *Levothyroxin restores hypothyroidism-induced impairment of hippocampus-dependent learning and memory: Behavioral, electrophysiological, and molecular studies*, in *Hippocampus*. 2009. p. 66-78. **Wrong population**

16. Appetecchia, M., *Effects on bone mineral density by treatment of benign nodular goiter with mildly suppressive doses of L-thyroxine in a cohort women study*, in *Horm Res*. 2005. p. 293-8. **Wrong population**

17. Arinzon, Z., et al., *Evaluation response and effectiveness of thyroid hormone replacement treatment on lipid profile and function in elderly patients with subclinical hypothyroidism*, in *Arch Gerontol Geriatr*. 2007. p. 13-19. **Related to topic but does not meet inclusion criteria**

18. Arrigo, T., et al., *Subclinical hypothyroidism: The state of the art*, in *Journal of endocrinological investigation*. 2008. p. 79-84. **Background - Review**

19. Atzmon, G., et al., *Extreme longevity is associated with increased serum thyrotropin*, in *J Clin Endocrinol Metab*. 2009. p. 1251-1254. **Background – Effect of elevated TSH**

20. Azizi, F., et al., *Reappraisal of the risk of iodine-induced hyperthyroidism: an epidemiological population survey*, in *J Endocrinol Invest*. 2005. p. 23-9. **Wrong population**

21. Bakiner, O., et al., *Subclinical hypothyroidism is characterized by increased QT interval dispersion among women*, in *Med Princ Pract*. 2008. p. 390-4. **No relevance to key questions; Wrong population**

22. Baldini, M., et al., *Neuropsychological functions and metabolic aspects in subclinical hypothyroidism: The effects of l-thyroxine*, in *Prog Neuro Psychopharmacol Biol Psychiatry*. 2009. p. 854-859. **Related to topic but does not meet inclusion criteria**

23. Bartalena, L., et al., *An update on the pharmacological management of hyperthyroidism due to Graves' disease.* Expert Opin Pharmacother, 2005. **6**(6): p. 851-61.**Wrong population**

24. Batrinos, M.L., *The problem of exogenous subclinical hyperthyroidism*, in *Hormones (Athens, Greece)*. 2006. p. 119-125.**Wrong population**

25. Bayer, M.F., J.A. Macoviak, and I.R. McDougall, *Diagnostic performance of sensitive measurements of serum thyrotropin during severe nonthyroidal illness: their role in the diagnosis of hyperthyroidism*, in *Clin Chem*. 1987. p. 2178-84. **Background**

26. Beltran, S., et al., *Subclinical hypothyroidism in HIV-infected patients is not an autoimmune disease*, in *Horm Res*. 2006. p. 21-6. **Wrong population**

27. Bensenor, I., *Screening for thyroid disorders in asymptomatic adults from Brazilian populations*, in *Sao Paulo Med J*. 2002. p. 146-51. **No data by design**

28. Berbel, P., et al., *Iodine supplementation during pregnancy: a public health challenge*, in *Trends Endocrinol Metab*. 2007. p. 338-43. **Wrong population**

29. Beyhan, Z., et al., *Restoration of euthyroidism does not improve cardiovascular risk factors in patients with subclinical hypothyroidism in the short term*, in *J Endocrinol Invest*. 2006. p. 505-10. **No relevance to key questions**

30. Bhasin, S., et al., *Sexual dysfunction in men and women with endocrine disorders*, in *Lancet*. 2007. p. 597-611. **No data by design; Wrong population**

31. Biondi, B., *Cardiovascular effects of mild hypothyroidism*, in *Thyroid*. 2007. p. 625-630. **No data by design**

32. Biondi, B. and D.S. Cooper, *The clinical significance of subclinical thyroid dysfunction*, in *Endocrine Reviews*. 2008. p. 76-131. **Background - Review**

33. Biondi, B. and I. Klein, *Hypothyroidism as a risk factor for cardiovascular disease*, in *Endocrine*. 2004. p. 1-13. **No data by design**

34. Biondi, B., et al., *Subclinical hyperthyroidism: clinical features and treatment options*, in *Eur J Endocrinol*. 2005. p. 1-9. **Background - Review; Wrong population**

35. Biondi, B., et al., *Effects of subclinical thyroid dysfunction on the heart*, in *Ann Intern Med*. 2002. p. 904-14. **Background – Complications of SCH**

36. Biondi, B., et al., *Subclinical hypothyroidism and cardiac function*, in *Thyroid*. 2002. p. 505-10. **Background – Complications of SCH**

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178. McMillan, C., et al., *Evaluation of new measures of the impact of hypothyroidism on quality of life and symptoms: the ThyDQoL and ThySRQ*, in *Value Health*. 2008. p. 285-94. **No relevance to key questions**

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181. Metso, S., et al., *Increased Cardiovascular and Cancer Mortality after Radioiodine Treatment for Hyperthyroidism*, in *J Clin Endocrinol Metab*. 2007. p. 2190-2196. **Wrong population**

182. Milionis, H., et al., *Thyroid substitution therapy induces high density lipoprotein-associated platelet-activating factor acetylhydrolase in patients with sub-clinical hypothyroidism: a potential antiatherogenic effect*, in *Thyroid*. 2005. p. 455-60. **Related to topic but does not meet inclusion criteria**

183. Mishra, T.K., et al., *Left ventricular dysfunction in patients with subclinical hypothyroidism and its reversibility after hormone therapy*, in *J Assoc Physicians India*. 2005. p. 943-6. **No relevance to key questions**

184. Monzani, F., et al., *Effect of levothyroxine replacement on lipid profile and intima-media thickness in subclinical hypothyroidism: a double-blind, placebo- controlled study*, in *J Clin Endocrinol Metab*. 2004. p. 2099-106. **Wrong population**

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186. Morocco, M. and R.T. Kloss, *Subclinical hypothyroidism in women: who to treat*, in *Dis Mon*. 2002. p. 659-70. **Background - Review**

187. Morote, J., et al., *Effect of androgen deprivation therapy in the thyroid function test of patients with prostate cancer*, in *Anti-Cancer Drugs*. 2005. p. 863-866. **No relevance to key questions**

188. Nakayama, Y., et al., *A case of transient 2:1 atrioventricular block, resolved by thyroxine supplementation for subclinical hypothyroidism*, in *Pacing Clin Electrophysiol*. 2006. p. 106-8. **Wrong population**

189. NCT00094237, *Subclinical Thyroid Dysfunction and Risk of Myocardial Infarction and Stroke*. **Related to topic but does not meet inclusion criteria**

190. NCT00497575, *Diagnosis and Follow-up of Patients With Subclinical Hypothyroidism (CHRO1)*. **Wrong population**

191. NCT00498238, *The Effect of Levothyroxine on Arterial Stiffness and Lipid Profile in Patients With Subclinical Hypothyroidism*. **No data by other parameter**

192. Nelson, M., et al., *Association Between Development of Hypothyroidism and Improved Survival in Patients With Head and Neck Cancer*, in *Arch Otolaryngol Head Neck Surg*. 2006. p. 1041-1046. **Wrong population**

193. Nyirenda, M.J., et al., *Thyroid Disease and Increased Cardiovascular Risk*, in *Thyroid*. 2005. p. 718-724. **Wrong population; No relevance to key questions**

194. Oflaz, H., et al., *Coronary flow reserve after L-thyroxine therapy in Hashimoto's thyroiditis patients with subclinical and overt hypothyroidism*, in *Endocrine*. 2007. p. 264-70. **Related to topic but does not meet inclusion criteria**

195. Osman, F., et al., *Heart rate variability and turbulence in hyperthyroidism before, during, and after treatment*, in *Am J Cardiol*. 2004. p. 465-9. **Wrong population**

196. O'Sullivan, A.J., M. Lewis, and T. Diamond, *Amiodarone-induced thyrotoxicosis: left ventricular dysfunction is associated with increased mortality*, in *Eur J Endocrinol*. 2006. p. 533-536. **Wrong population**

197. Ovadia, S., L. Lysyy, and T. Zubkov, *Pericardial effusion as an expression of thyrotoxicosis*, in *Tex Heart Inst J*. 2007. p. 88-90. **No relevance to key questions; Wrong population**

198. Ozcan, O., et al., *The effects of thyroxine replacement on the levels of serum asymmetric dimethylarginine (ADMA) and other biochemical cardiovascular risk markers in patients with subclinical hypothyroidism*, in *Clin Endocrinol (Oxf)*. 2005. p. 203-6. **Wrong population**

199. Pagano, L., et al., *Coronary Flow Reserve (CFR) in Patients with Subclinical Hypothyroidism*, in *32nd Annual Meeting of the European Thyroid Association, Carl Ludwig Institute, University Hospital Leipzig, Leipzig (Germany), 1-5 Sep 2007*. 2007. p. 90. **No relevance to key questions**

200. Palmieri, E.A., et al., *Subclinical hypothyroidism and cardiovascular risk: a reason to treat?*, in *Treat Endocrinol*. 2004. p. 233-44. **Background - Review; No data by design**

201. Papi, G., et al., *A clinical and therapeutic approach to thyrotoxicosis with thyroid-stimulating hormone suppression only*, in *American Journal of Medicine*. 2005. p. 349-361. **Background - Review**

202. Papi, G., et al., *Subclinical hypothyroidism*, in *Curr Opin Endocrinol Diabetes Obes*. 2007. p. 197-208. **Background - Review**

203. Park, Y.J., et al., *Subclinical hypothyroidism might increase the risk of transient atrial fibrillation after coronary artery bypass grafting*, in *Ann Thorac Surg*. 2009. p. 1846-52. **Wrong population**

204. Parker, L., *Subclinical hyperthyroidism*, in *N Engl J Med*. 2002. p. 67-8. **No data by design**

205. Paz-Filho, G.J. and H. Graf, *Recombinant human thyrotropin in the management of thyroid disorders*, in *Expert Opinion on Biological Therapy*. 2008. p. 1721-1732. **Wrong population; No relevance to key questions**

206. Pearce, E.N., *Hypothyroidism and dyslipidemia: Modern concepts and approaches*, in *Current Cardiology Reports*. 2004. p. 451-456. **No data by design**

207. Pearce, E.N., *Thyroid dysfunction in perimenopausal and postmenopausal women*, in *Menopause Int*. 2007. p. 8-13. **No data by design**

208. Peppa, M., et al., *Insulin Resistance and Oxidative Stress Induce Advanced Glycation End Products Formation in Patients with Clinical and Subclinical Hypothyroidism*, in *10th European Congress of Endocrinology (ECE 2008), Berlin (Germany), 3-7 May 2008*. 2008. **No relevance to key questions**

209. Perez, A., et al., *Emerging cardiovascular risk factors in subclinical hypothyroidism: lack of change after restoration of euthyroidism*, in *Metabolism*. 2004. p. 1512-5. **Wrong population; No relevance to key questions**

210. Pietras, S.M. and J.D. Safer, *Diagnostic confusion attributable to spurious elevation of both total thyroid hormone and thyroid hormone uptake measurements in the setting of autoantibodies: case report and review of related literature*, in *Endocr Pract*. 2008. p. 738-42. **Background - Review**

211. Pimentel, L. and K.N. Hansen, *Thyroid disease in the emergency department: A clinical and laboratory review*, in *Journal of Emergency Medicine*. 2005. p. 201-209. **No data by design; No relevance to key questions**

212. Pingitore, A. and G. Iervasi, *Triiodothyronine (T3) effects on cardiovascular system in patients with heart failure*, in *Recent Pat Cardiovasc Drug Discov*. 2008. p. 19-27. **Background - Review; No data by design**

213. Portella, R.B., et al., *Exercise performance in young and middle-aged female patients with subclinical hyperthyroidism*, in *Thyroid*. 2006. p. 731-735. **No relevance to key questions**

214. Premawardhana, L.D.K.E. and J.H. Lazarus, *Management of thyroid disorders*, in *Postgraduate Medical Journal*. 2006. p. 552-558. **Background - Review**

215. Radacsi, A., et al., *Mortality rate of chronically ill geriatric patients with subnormal serum thyrotropin concentration: a 2-yr follow-up study*, in *Endocrine*. 2003. p. 133-6. **No relevance to key questions; Wrong population**

216. Rao, P., O. Pereira, and J. Weaver, *The Outcome of the Management of Subclinical Hyperthyroidism: Use of Fixed Dose of Radioiodine Therapy*, in *2007 BES Conference of the Society for Endocrinology, International Convention Centre, Birmingham (UK), 5-8 Mar 2007*. 2007. **Related to topic but does not meet inclusion criteria**

217. Rasic-Milutinovic, Z., et al., *Subclinical Hypothyroidism and Bone Mineral Density*, in *10th European Congress of Endocrinology (ECE 2008), Berlin (Germany), 3-7 May 2008*. 2008. **No relevance to key questions**

218. Razvi, S., C.V. McMillan, and J.U. Weaver, *Quality of Life, Health Status, Symptoms and Treatment Satisfaction in Subclinical Hypothyroidism: A Double&Hyphen;Blind 12-Week Cross&Hyphen;Over Study of L-Thyroxine Versus Placebo*, in *8th European Congress of Endocrinology (ECE 2006), SECC Congress Centre, Glasgow, Scotland (UK), 1-5 Apr 2006*. 2006. **Related to topic but does not meet inclusion criteria**

219. Razvi, S., S. Pearce, and J. Weaver, *Does L-Thyroxine Reduce Weight in People with Subclinical Hypothyroidism?*, in *197th Meeting of the Society for Endocrinology, Kensington Town Hall, London (UK), 6-7 Nov 2006*. 2006. **Related to topic but does not meet inclusion criteria**

220. Razvi, S. and J.U. Weaver, *Subclinical hypothyroidism and cardiovascular risk*, in *Thyroid*. 2004. p. 870; author reply 871-2. **No data by design**

221. Razvi S, I.L., McMillan CV, Weaver JU., *Health status in patients with sub-clinical hypothyroidism.*, in *Eur J Endocrinol.* . 2005 May. p. 713-7. **No relevance to key questions**

222. Razvi, S.e.a., *Incident ischemic heart disease and thyroid status: The Whickham cohort reevaluated*, in *Thyroid*. 2007. p. S-72 #89. **No data by design**

223. Rege, V., et al., *Comparison of Kodak Amerlite FT4 and TSH-30 with T4 and TSH as first-line thyroid function tests*, in *Clin Biochem*. 1996. p. 1-4. **Background**

224. Resta, O., et al., *Influence of subclinical hypothyroidism and T4 treatment on the prevalence and severity of obstructive sleep apnoea syndrome (OSAS)*, in *J Endocrinol Invest*. 2005. p. 893-8. **Wrong population**

225. Reverter, J.L., et al., *Lack of deleterious effect on bone mineral density of long-term thyroxine suppressive therapy for differentiated thyroid carcinoma*, in *Endocr Relat Cancer*. 2005. p. 973-81. **Wrong population**

226. Roberts, C.G. and P.W. Ladenson, *Hypothyroidism*, in *Lancet*. 2004. p. 793-803. **Background - Review**

227. Roti, E., et al., *Are thyroid function tests too frequently and inappropriately requested?*, in *J Endocrinol Invest*. 1999. p. 184-90. **Background - Review**

228. Sait Gonen, M., et al., *Assessment of anxiety in subclinical thyroid disorders*, in *Endocr J*. 2004. p. 311-5. **No relevance to key questions**

229. Sakaki, T., et al., *Cardiac wall motion abnormalities observed in a patient with transient hyperthyroidism*, in *Japanese Heart Journal*. 2004. p. 1071-1077. **Wrong population**

230. Saler, T., et al., *The Effect of L-Thyroxin Theraphy on Left Ventricular Diastolic Dysfunction in Patients with Subclinical Hypothyroidism*, in *9th European Congress of Endocrinology (ECE 2007), Budapest (Hungary), 28 Apr-2 May 2007*. **No relevance to key questions**

231. Samuels, M.H., *Cognitive function in untreated hypothyroidism and hyperthyroidism*, in *Curr Opin Endocrinol Diabetes Obes*. 2008. p. 429-33. **No relevance to key questions**

232. Samuels, M.H., et al., *Health status, mood, and cognition in experimentally induced subclinical hypothyroidism*, in *J Clin Endocrinol Metab*. 2007. p. 2545-51.**Wrong population**

233. Santhana Krishnan, S.G., et al., *Falsely raised TSH levels due to human anti-mouse antibody interfering with thyrotropin assay*, in *Postgrad Med J*. 2006. p. e27. **No relevance to key questions; No data by design**

234. Schiff, G.D., et al., *Missed hypothyroidism diagnosis uncovered by linking laboratory and pharmacy data*, in *Arch Intern Med*. 2005. p. 574-7. **Wrong population**

235. Sengul, E., et al., *Homocysteine concentrations in subclinical hypothyroidism*, in *Endocr Res*. 2004. p. 351-9. **No relevance to key questions**

236. Serter, R., et al., *The effect of L-thyroxine replacement therapy on lipid based cardiovascular risk in subclinical hypothyroidism*, in *J Endocrinol Invest*. 2004. p. 897-903. **Related to topic but does not meet inclusion criteria**

237. Sgarbi, J.A., et al., *The effects of early antithyroid therapy for endogenous subclinical hyperthyroidism in clinical and heart abnormalities*, in *J Clin Endocrinol Metab*. 2003. p.1672-7. **No relevance to key questions**

238. Shinno, H., et al., *Successful treatment with levothyroxine for idiopathic hypersomnia patients with subclinical hypothyroidism*, in *General Hospital Psychiatry*. 2009. p. 190-193. **No data by design**

239. Siegmund, W., et al., *Replacement therapy with levothyroxine plus triiodothyronine (bioavailable molar ratio 14 : 1) is not superior to thyroxine alone to improve well-being and cognitive performance in hypothyroidism*, in *Clin Endocrinol (Oxf)*. 2004. p. 750-7. **Wrong population**

240. Simonsick, E.M., et al., *Subclinical Hypothyroidism and Functional Mobility in Older Adults*, in *Arch Intern Med*. 2009. p. 2011-2017. **Background – Effect of elevated TSH**

241. Smit, J.W.A., et al., *Reversible diastolic dysfunction after long-term exogenous subclinical hyperthyroidism: A randomized, placebo-controlled study*, in *Journal of Clinical Endocrinology and Metabolism*. 2005. p. 6041-6047. **Wrong population**

242. Snabboon, T., et al., *A more appropriate algorithm of thyroid function test in diagnosis of hyperthyroidism for Thai patients*, in *J Med Assoc Thai*. 2004. p. S19-21. **Wrong population**

243. Spencer, C.A., et al., *National Health and Nutrition Examination Survey III Thyroid-Stimulating Hormone (TSH)-Thyroperoxidase Antibody Relationships Demonstrate That TSH Upper Reference*

Limits May Be Skewed by Occult Thyroid Dysfunction, in *J Clin Endocrinol Metab*. 2007. p. 4236-4240. **Background - Review**

244. Squizzato, A., et al., *Subclinical hypothyroidism and deep venous thrombosis. A pilot cross-sectional study*, in *Thromb Haemost*. 2007. p. 803-6. **No relevance to key questions**

245. Surks, M.I., *Commentary: subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society*, in *J Clin Endocrinol Metab*. 2005. p.586-587. **Background - Review**

246. Surks, M.I., *Primary hypothyroidism: new issues and controversies.* , in *Endocrinologist*. 2006. p. 203-207. **No data by design**

247. Surks, M.I., G. Goswami, and G.H. Daniels, *The thyrotropin reference range should remain unchanged*, in *Journal of Clinical Endocrinology and Metabolism*. 2005. p. 5489-5496. **No data by design**

248. Surks, M.I. and J.G. Hollowell, *Age-Specific Distribution of Serum Thyrotropin and Antithyroid Antibodies in the U.S. Population: Implications for the Prevalence of Subclinical Hypothyroidism*, in *J Clin Endocrinol Metab*. 2007. p. 4575-4582. **Background**

249. Taddei, S., et al., *Impaired Endothelium-Dependent Vasodilatation in Subclinical Hypothyroidism: Beneficial Effect of Levothyroxine Therapy*, in *J Clin Endocrinol Metab*. 2003. p. 3731-3737. **Related to topic but does not meet inclusion criteria**

250. Teixeira, P., et al., *Serum leptin in overt and subclinical hypothyroidism: effect of levothyroxine treatment and relationship to menopausal status and body composition.*, in *Thyroid*. 2009. p. 443-50. **Related to topic but does not meet inclusion criteria**

251. Teixeira Pde, F., et al., *Lipid profile in different degrees of hypothyroidism and effects of levothyroxine replacement in mild thyroid failure*, in *Transl Res*. 2008. p. 224-31. **Wrong population**

252. Teixeira, P.F., et al., *Treatment of subclinical hypothyroidism reduces atherogenic lipid levels in a placebo-controlled double-blind clinical trial*, in *Horm Metab Res*. 2008. p. 50-5. **Wrong population**

253. Trokoudes, K.M., N. Skordis, and M.K. Picolos, *Infertility and thyroid disorders*, in *Curr Opin Obstet Gynecol*. 2006. p. 446-51. **No data by design**

254. Turhan, S., et al., *Effects of thyroxine therapy on right ventricular systolic and diastolic function in patients with subclinical hypothyroidism: a study by pulsed wave tissue Doppler imaging*, in *J Clin Endocrinol Metab*. 2006. p. 3490-3. **Wrong population; No relevance to key questions**

255. Unal, O., et al., *Effect of levothyroxine treatment on QT dispersion in patients with subclinical hypothyroidism*, in *Endocr Pract*. 2007. p. 711-5. **Related to topic but does not meet inclusion criteria**

256. Vaidya, B., et al., *Radioiodine treatment for benign thyroid disorders: results of a nationwide survey of UK endocrinologists*, in *Clin Endocrinol (Oxf)*. 2008. p. 814-20. **No relevance to key questions**

257. Vaisman, M., et al., *Effects of Levothyroxine Reposition on Insulin Sensitivity, Leptin Levels and Fat Mass in Patients with Subclinical Hypothyroidism*, in *32nd Annual Meeting of the European Thyroid Association, Carl Ludwig Institute, University Hospital Leipzig, Leipzig (Germany), 1-5 Sep 2007*. 2007. p. 75. **Related to topic but does not meet inclusion criteria**

258. van den Beld, A.W., et al., *Thyroid Hormone Concentrations, Disease, Physical Function, and Mortality in Elderly Men*, in *J Clin Endocrinol Metab*. 2005. p. 6403-6409. **Background – effect of elevated TSH**

259. Vanderpump, M., *Subclinical hypothyroidism: the case against treatment*, in *Trends Endocrinol Metab*. 2003. p. 262-6. **Background - Review**

260. Velia-Asimi, Z. and B. Heljic, *Changes in Cystatin C during the Treatment of Subclinical Hypothyroidism*, in *10th European Congress of Endocrinology (ECE 2008), Berlin (Germany), 3-7 May 2008*. 2008. **No relevance to key questions**

261. Velija-Asimi, Z. and J. Karamehic, *The effects of treatment of subclinical hypothyroidism on metabolic control and hyperinsulinemia*, in *Med Arh*. 2007. p. 20-1. **Related to topic but does not meet inclusion criteria**

262. Vergara, P., et al., *Evaluation of thyroid dysfunction in patients with paroxysmal atrial fibrillation*, in *Anadolu Kardiyoloji Dergisi*. 2007. p. 104-106. **No relevance to key questions**

263. Villar, H. and H. Gharib, *Review: Available evidence does not support a benefit for thyroid hormone replacement in adults with subclinical hypothyroidism: Commentary*, in *Evidence-Based Medicine*. 2008. p. 22%N 1. **No data by design**

264. Volzke, H., M. Dorr, and H. Wallaschofski, *Is Subclinical Hyperthyroidism Associated with Blood Pressure and Hypertension?*, in *8th European Congress of Endocrinology (ECE 2006), SECC Congress Centre, Glasgow, Scotland (UK), 1-5 Apr 2006*. 2006. **No relevance to key questions**

265. Volzke, H., et al., *Review: The association of thyroid dysfunction with all-cause and circulatory mortality: is there a causal relationship?*, in *J Clin Endocrinol Metab*. 2007. p. 2421-9. **No data by design**

266. Waise, A. and H.C. Price, *The upper limit of the reference range for thyroid-stimulating hormone should not be confused with a cut-off to define subclinical hypothyroidism*, in *Ann Clin Biochem*. 2009. p. 93-8. **Background – Effect of elevated TSH**

267. Walsh, J.P., et al., *Subclinical thyroid dysfunction and blood pressure: a community-based study*, in *Clin Endocrinol (Oxf)*. 2006. p. 486-91. **No data by design**

268. Wartofsky, L. and R.A. Dickey, *The evidence for a narrower thyrotropin reference range Is compelling*, in *J Clin Endocrinol Metab*. 2005. p. 5483-5488. **No data by design**

269. Wartofsky, L., D. Van Nostrand, and K.D. Burman, *Overt and 'subclinical' hypothyroidism in women*, in *Obstet Gynecol Surv*. 2006. p. 535-42. **Background - Review; No data by design**

270. Weetman, A.P., *Radioiodine treatment for benign thyroid diseases*, in *Clin Endocrinol (Oxf)*. 2007. p. 757-64. **No relevance to key questions**

271. Weise, A.M., C.Y. Liu, and A.F. Shields, *Fatal liver failure in a patient on acetaminophen treated with sunitinib malate and levothyroxine*, in *Annals of Pharmacotherapy*. 2009. p. 761-766. **Wrong population**

272. Weissel, M., *Disturbances of thyroid function in the elderly*, in *Wien Klin Wochenschr*. 2006. p. 16-20. **No data by design**

273. Wilson, G.R. and R.W. Curry, Jr., *Subclinical thyroid disease*, in *Am Fam Physician*. 2005. p. 1517-24. **Background - Review; No data by design**

274. Woeber, K., *Observations concerning the natural history of subclinical hyperthyroidism*, in *Thyroid*. 2005. p. 687. **No relevance to key questions**

275. Yandell, S.D., et al., *Radioiodine studies, low serum thyrotropin, and the influence of statin drugs*, in *Thyroid*. 2008. p. 1039-42. **No relevance to key questions**

276. Yavuz, D.G., et al., *Exogenous subclinical hyperthyroidism impairs endothelial function in nodular goiter patients*, in *Thyroid*. 2008. p. 395-400. **Wrong population**

277. Yavuz, D.G., et al., *Association of serum paraoxonase activity with insulin sensitivity and oxidative stress in hyperthyroid and TSH-suppressed nodular goitre patients.* Clin Endocrinol (Oxf), 2004. **61**(4): p. 515-21. **No relevance to key questions; Wrong population**

278. Yazici, M., et al., *Effects of thyroxin therapy on cardiac function in patients with subclinical hypothyroidism: index of myocardial performance in the evaluation of left ventricular function*, in *Int J Cardiol*. 2004. p. 135-43. **Wrong outcome**

279. Zargar, A.H., et al., *Prevalence and pattern of sick euthyroid syndrome in acute and chronic non-thyroidal illness--its relationship with severity and outcome of the disorder*, in *The Journal of the Association of Physicians of India*. 2004. p. 27-31. **No relevance to key questions**

280. Zhu, D.-F., et al., *fMRI revealed neural substrate for reversible working memory dysfunction in subclinical hypothyroidism*, in *Brain*. 2006. p. 2923-2930. **Related to topic but does not meet inclusion criteria**

281. Zwirska-Korczala, K., et al., *Influence of thyroxine on serum soluble interleukin-2 receptor alpha levels in thyroid disorders*, in *J Clin Pharm Ther*. 2004. p. 151-6. **Wrong population**

[*]- Related to topic but does not meet inclusion criteria includes uncompleted trials and studies that did not meet inclusion criteria for quality or study design.
- No data by design includes reviews or systematic reviews.

Appendix D

Supplemental Text and Tables

Table D3. Screening and case-finding recommendations of other groups

Organization	Guideline
ATA 2000 [Ladenson 2000]	Adults should be screened for thyroid dysfunction by measurement of the serum thyrotropin concentration, beginning at age 35 years and every 5 years thereafter.
IOM, 2003[12]	There is insufficient evidence to recommend periodic, routine screening for thyroid dysfunction among asymptomatic persons using serum TSH levels.
USPSTF 2004 [Ann Intern Med. 2004;140:125-127]	Evidence is insufficient to recommend for or against routine screening for thyroid disease in adults
AACE, ATA, Endocrine Society, 2004 [Surks 2004]	The panel recommends against population-based screening for thyroid disease. Case ascertainment in certain high risk groups is encouraged. The panel finds the evidence insufficient to recommend for or against routine determination of TSH levels (screening) in pregnant women or women planning to become pregnant. It is reasonable to consider serum TSH measurement for women with a family history of thyroid disease, prior thyroid dysfunction symptoms or physical findings suggestive of hypothyroidism or hyperthyroidism, an abnormal thyroid gland on examination, type 1 diabetes mellitus, or a personal history of an autoimmune disorder.
AACE, ATA, Endocrine Society, 2004 [Gharib 2005]	Consensus statement favors routine screening for subclinical thyroid dysfunction in adults, including pregnant women and those contemplating pregnancy
British Thyroid Association 2006	• If screening is performed, and a high serum TSH concentration and normal FT4 is found, repeat measurement 3-6 months later after excluding non-thyroidal illness and drug interference. • If the TSH is mildly elevated (above the reference range but below 10 mU/L), obtain serum thyroid peroxidase antibodies. • If antibody levels are high, repeat measurement of TSH annually. If they are low, repeat measurement of TSH every 3 years. Initiate treatment if the TSH level is greater than 10 mU/L or the patient develops clinical findings of hypothyroidism.
ACOG, 2007[ACOG Committee Opinion No. 381: Subclinical Hypothyroidism in Pregnancy]	Based on current literature, thyroid testing in pregnancy should be performed on symptomatic women and those with a personal history of thyroid disease or other medical conditions associated with thyroid disease (eg, diabetes mellitus). Without evidence that identification and treatment of pregnant women with subclinical hypothyroidism improves maternal or infant outcomes, routine screening for subclinical hypothyroidism currently is not recommended.
AAFP [AAFP web site accessed 1/4/2010]	The AAFP concludes that the evidence is insufficient to recommend for or against routine screening for thyroid disease in adults.
ACP [web site accessed 1/4/2010]	No current guidelines. Recommends reviewing guidelines of USPSTF.

Abbreviations:

AACE: American Association of Clinical Endocrinologists
AAFP: American Academy of Family Physicians
ACOG: American Congress of Obstetricians and Gynecologists
ACP: American College of Physicians
ATA: American Thyroid Association
IOM: Institute of Medicine

Table D4. Findings of the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society Panel.

Complication	Strength of Evidence	Benefits and Harms of Treatment
Progression to overt hypothyroidism	Good	Variable
Adverse cardiac end points	Insufficient	No evidence
Elevation in serum cholesterol and LDL-C levels	Insufficient	Insufficient
Cardiac dysfunction	Insufficient	Insufficient
Symptoms of hypothyroidism	No clear evidence	Insufficient
Psychiatric symptoms	No clear evidence	Insufficient

(Adapted from JAMA {Surks, 2004 #237}.)

TABLE D5. Results of Search for Systematic Reviews

1. Thyroid disease in pregnancy. ACOG Technical Bulletin Number 181--June 1993. Int J Gynaecol Obstet. 1993 Oct;43(1):82-8.

2. Abraham P, Avenell A, Watson WA, Park CM, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. Cochrane Database of Systematic Reviews2009.

3. Ahangari Z, Nasser M, Mahdian M, Marchesan MA, Fedorowicz Z. Interventions for the management of external root resorption. Cochrane Database of Systematic Reviews2009.

4. Angermayr L, Clar C. Iodine supplementation for preventing iodine deficiency disorders in children. Cochrane Database of Systematic Reviews2009.

5. Ardaillou R, Le Gall JY, Commission IdlANdM. [Mass neonatal screening using biological testing]. Gynecol Obstet Fertil. 2007/04/03 ed2007. p. 367-74.

6. Balaguer A, Escribano J, Feliu A, Roque i Figuls M. Dietary interventions for preventing complications in idiopathic hypercalciuria. Cochrane Database of Systematic Reviews2009.

7. Balogh R, Ouellette-Kuntz H, Bourne L, Lunsky Y, Colantonio A. Organising health care services for persons with an intellectual disability. Cochrane Database of Systematic Reviews2009.

8. Barrington KJ, Brion LP. Dopamine versus no treatment to prevent renal dysfunction in indomethacin-treated preterm newborn infants. Cochrane Database of Systematic Reviews2009.

9. Baskin HJ, Cobin RH, Duick DS, Gharib H, Guttler RB, Kaplan MM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract. 2004/07/21 ed2002. p. 457-69.

10. Biondi B, Palmieri EA, Lombardi G, Fazio S. Effects of subclinical thyroid dysfunction on the heart. Ann Intern Med. 2002/12/03 ed2002. p. 904-14.

11. Bjorndal MM, Sandmo Wilhelmsen K, Lu T, Jorde R. Prevalence and causes of undiagnosed hyperthyroidismin an adult healthy population. The Tromso study. J Endocrinol Invest. 2008/12/19 ed2008. p. 856-60.

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Table D6. Systematic Review Study Concordance

Study	Ref	Design	Tanis 1996	Danese 2000	Peng 2007	Surks 2004	Helfand 2004	Villar 2007	Rugge 2010
Nilsson, G., Nordlander, S. & Levin, K., 1976	36		X						
Bantle, J.P. et al., 1981	3		X						
Forfar, J. et al., 1981	17					X			
LITHELL, H. et al., 1981	27		X						
RIDGWAY, E.C. et al., 1981	42		X						
BELL, G.M. et al., 1985	4		X	X					
Grund, F.M. & Niewoehner, C.B., 1989	19					X			
Arem, R. & Patsch, W., 1990	2		X	X					
CARON, P. et al., 1990	9		X	X					
Elder, J. et al., 1990	12		X						
Bogner, U. et al., 1993	5		X	X					
Franklyn, J.A. et al., 1993	18		X	X					
Johnston, J., McLelland, A. & O'Reilly, D.S., 1993	23		X						
Parle, J.V. et al., 1993	39					X			
Mudde, A.H., Houben, A.J.H.M. & Kruseman, A.C.N., 1994	34					X			
Arem, R. et al., 1995	1			X					
Fazio, S. et al., 1995	16					X			
Faber et al., 1998	14					X			
Monzani, F. et al., 1999	32					X			
Kumeda, Y. et al., 2000	26					X			
Pantazi, H. & Papapetrou, P.D., 2000	38					X			
Faber, J. et al., 2001	15					X			
COOPER, D.S. et al., 1984	10	RCT	X	X	X	X	X	X	X
NYSTRÖM, E. et al., 1988	37	RCT	X			X	X	X	X
ROSS, D.S., DANIELS, G.H. & GOUVEIA, D., 1990	43	RCT				X		X	X
Jaeschke, R. et al., 1996	22	RCT		X			X	X	X
Michalopoulou, G. et al., 1998	29	RCT					X		X
Meier, C. et al., 2001	28	RCT			X	X	X	X	X
Monzani, F. et al., 2001	33	RCT						X	X
Pollock, M.A. et al., 2001	40	RCT					X		X
Caraccio, N., Ferrannini, E. & Monzani, F., 2002	7	RCT			X		X	X	X
Kong, W.M. et al., 2002	25	RCT			X	X	X	X	X
Yonem, O. et al., 2002	45	RCT (Hyper)							**X**
Monzani, F. et al., 2004	31	RCT			X			X	X
Yazici, M. et al., 2004	44	RCT						X	X
Caraccio, N. et al., 2005	8	RCT						X	**X**
IQBAL, A., JORDE, R. & FIGENSCHAU, Y., 2006	21	RCT			X				**X**
Jorde, R. et al., 2006	24	RCT						X	**X**
Buscemi, S. et al., 2007	6	RCT (Hyper)							**X**
Razvi, S. et al., 2007	41	RCT							**X**
Mikhail, G.S. et al., 2008	30	RCT							**X**
Nagasaki, T. et al., 2009	35	RCT							**X**

Concordance References

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Table D7. Description and results of randomized trials of thyroxine replacement therapy from Helfand 2004

Study Year	Study design	Patients	Setting	Age Gender	Eligibility criteria	Other population characteristics
Known history of thyroid disease						
Cooper 1984	Randomized, double-blind placebo controlled trial.	Previously treated Graves' disease, stage c subclinical hypothyroidism	Thyroid specialty clinic, Boston	32 women and 1 man, mean age 55 years	TSH>3.5 mU/L on 2 occasions	History of Graves' disease
Meier 2001	Double-blind placebo controlled trial.	Autoimmune thyroiditis (n=33), previously treated Graves' disease (n=22), previously treated goiter (7)	Thyroid specialty clinic, Switzerland	63 women, mean age 58.5±1.3 years	Women 18-75 years; TSH> 6.0 mU/L on 2 occasions; exaggerated TSH response to TRH; good general health	History of autoimmune thyroiditis (n=33), Graves' disease (n=22), goiter (n=7). Only 4 had idiopathic subclinical hypothyroidism
Caraccio 2002	Unblinded placebo-controlled randomized trial.	Hashimoto's thyroiditis (48) or Graves' disease (1)	Medical school internal medicine clinic, Italy	42 premenopausal women, 7 men	TSH>3.6 mU/L for >6 months, + atP and anti-Tg, good general health	SCH patients had higher TC, LDL, and ApoB levels than healthy controls

Study, year	Exclusion criteria	Funding sources and role of funder	Interventions (dose, duration)	Control	Baseline TSH	Number screened/ eligible/ enrolled	Number withdrawn/ analyzed
Known history of thyroid disease							
Cooper 1984	None stated	U.S. PHS (Armour supplied LT4)	LT4 50 micrograms then titrated up	Placebo	11 (mean) 3.6-55.3 (range) mean TSH in control group increased to ~15 by the end of the study	656/91/41	8/33
Meier 2001	Coronary heart disease, lipid-lowering drugs, history of poor compliance. (Estrogen therapy allowed.)	Swiss Research Foundation, Henning Berlin, Sandoz, Roche	LT4 titrated over 6 months (mean final dose 85.5 ±4.3), with similar visits and changes in control group. Total followup 50 weeks	Placebo	12.8 (mean) 5-50 (range)	NR/NR/66	3/63
Caraccio 2002	Diabetes, renal or liver disease, TC>7.8 mmol/L	Grant from University	LT4 25 then titrated up	Placebo	5.43 (mean) 3.65-15 (range)	NR/NR/49	0/49

Study, year	Outcomes assessed/ when assessed	How outcomes assessed (e.g., scales used)	LT4 vs. Placebo group results	Before/after results
Known history of thyroid disease				
Cooper, 1984	Symptoms, Lipid profile at 1 year	Symptom change scores ("Cooper questionnaire")	Improved symptoms (-1.2 vs. +2.1) in LT4 group. 47% improved in LT4 group vs. 19% in placebo group (NNT=3.6). No difference in lipid profiles	Placebo group's TSH and symptoms rose during the year, suggesting the patients had rapidly advancing subclinical hypothyroidism
Meier, 2001	Symptoms, Lipid profile at 1 year	Thyroid symptom questionnaire	Post-treatment LDLc was the same in both groups (3.7±0.2, p=0.11), and symptoms scores were not significantly different (p=.53)	LDLc reduced from 4.0 to 3.7 in the LT4 group (p=0.004) and there were borderline improvements in symptom scores (p=0.02). Placebo group TSH was stable
Caraccio, 2002	Lipid profile at 6 months for placebo group vs. about 11 months for LT4 group	Biochemical tests	There were no significant differences between LT4 and placebo groups in any lipid parameter	LT4 group: TC reduced from 5.5 to 5.0; LDLc from 3.6 to 3.1

Study, year	Adverse effects assessed?	Adverse effects	Quality rating (good/fair/poor)	Relevance to screening	Comments	Questions
Known history of thyroid disease						
Cooper, 1984	Only through symptom scores	4 patients in LT4 group felt worse, vs. 6 in placebo group	Good	Low	Well-conducted trial, but subjects had known thyroid disease and the study is not relevant to screening	
Meier, 2001	No formal assessment done		Poor	Low	The discrepency between before/after results and LT4 vs. placebo results suggests that randomization was probably flawed	Were patients informed of their LDLc levels?
Caraccio, 2002	Not assessed		Poor	Fair	Analyzed as an open, uncontrolled study	Was completion of the study a criterion for inclusion in the analysis? How many patients were screened, eligible, enrolled, and randomized? Were patients & providers aware of treatment? How was randomization done? Were baseline differences statistically significant? What proportion of subjects in each group had a TC>6.2?

Study Year	Study design	Patients	Setting	Age Gender	Eligibility criteria	Other population characteristics
No known history or not stated						
Jaeschke 1996	Randomized, double-blind placebo controlled trial.	Diagnosis of subclinical hypothyroidism	Unclear setting, Ontario	28 women and 9 men over age 55, mean age 68 years	TSH> 6 mU/L on 2 occasions	
Kong 2002	Randomized, double-blind placebo controlled trial.	Women with a diagnosis of subclinical hypothyroidism	Referrals from GPs for thyroid function tests, London	45 women, mean age ~49 years	Women over 18 years; 5<TSH<10 mU/L	Most patients were referred because of symptoms
Nystrom 1988	Randomized, double-blind placebo controlled crossover trial.	Women identified by screening	Population-based screening study, Gothenburg	20 women, aged 51-73	Women over 18 years; 4<TSH<15 mU/L, exaggerated TSH response to TRH	Symptoms did not differ between subjects and healthy controls

Study, year	Exclusion criteria	Funding sources and role of funder	Interventions (dose, duration)	Control	Baseline TSH	Number screened/ eligible/ enrolled	Number withdrawn/ analyzed
No known history or not stated							
Jaeschke 1996	Medications that interfere with TFTs; serious medical conditions	Ontario Ministry of Health, Boots Pharmaceuticals	LT4 25 then titrated up (mean final dose 68±21)	Placebo	9.4 (mean) 6-32 (range)	NR/NR/37	6/31
Kong 2002	History of thyroid disease, psychiatric disorder, anticipated pregnancy	Medical Research Council	LT4 50 then titrated up to 100 if TSH>6 mU/L.	Placebo	~7.7 (mean)	NR/52/45	10/34 (for quality-of-life) 18/27 for lipids
Nystrom 1988	History of or signs of thyroid disease, history of cardiovascular disease	Non-industry grants (Nyegaard supplied LT4)	LT4 50 for 2 weeks, then 100 mg for 2 wks, then 150 daily	Placebo	~7.7 (mean) 2.9-16.3 (range)	1,192/22/20	3/17

Study, year	Outcomes assessed/ when assessed	How outcomes assessed (e.g., scales used)	LT4 vs. Placebo group results	Before/after results
No known history or not stated				
Jaeschke, 1996	Quality of Life, Symptoms, Lipid profile at 6 months	Chronic Thyroid Questionnaire, Cooper questionnaire, SIP, cognitive tests	No improvement in symptoms or lipids. Improved memory in LT4 group (mean difference of .58 on z score scale, described as "small and of questionable clinical importance")	Placebo group's TSH rose from 9.42 to 10.32 over 6 months
Kong, 2002	Quality of Life, Symptoms, Lipid profile at 6 months.	Thyroid symptom questionnaire, GHQ-30, HADS	No improvement in symptoms or lipids	Placebo group's TSH dropped from 7.3 to 5.6 over 6 months
Nystrom, 1988	Quality of Life, Symptoms, Psychometric Tests, Vital signs, ECG, Lipid profile at 6 months.	Thyroid symptom questionnaire, reaction time, Bingley's memory test	No difference in lipids. In before/after comparisons, symptom scores improved by the equivalent of 1 symptom per subject ($p<0.001$), and 4 patients felt better with LT4 than with placebo.	

Study, year	Adverse effects assessed?	Adverse effects	Quality rating (good/fair/poor)	Relevance to screening	Comments	Questions
No known history or not stated						
Jaeschke, 1996	Only through dropouts	1 case of atrial fibrillation and 1 case of angina in LT4 group	Fair	Fair	Description of recruitment was inadequate	Were patients referred from family practitioners? Were patients who had a history of thyroid disease included?
Kong, 2002	Only through symptom scores	Anxiety scores were higher in the LT4 group	Poor	Fair	High dropout rate, but patients were relevant to primary care: symptomatic with borderline TSH values	
Nystrom, 1988	Only through dropouts.	In LT4 group, 1 subject dropped out because of nervousness, one because of a sense of tachycardia	Poor	Good	The flaws in analyzing data make the study uninterpretable, but the patients are most like those encountered in screening	

Study Year	Study design	Patients	Setting	Age Gender	Eligibility criteria	Other population characteristics
Biochemically euthyroid patients						
Michalopoulou 1998	Randomized trial with active control group.	Patients referred for lipid assessment	Preventive Medicine (Lipid) hospital-based clinic, Greece	Not stated.	TC>7.5 mmol/L and TSH 0.4-4.0 mU/L	
Pollack 2001	Double-blind placebo controlled randomized crossover trial.	Symptomatic patients with normal TSH and T4	Referrals from GPs, hospital clinic, and response to newspaper ad, Glasgow	25 symptomatic and 19 asymptomatic subjects, sex and age not given	"Recent thyroid function tests within the reference range" plus (a) at least 3 symptoms of hypothyroidism (tiredness, lethargy, weight gain, or 3 others) or (b) no symptoms	Symptomatic subjects weighed more and had worse memory and psychological function than healthy controls

Study, year	Exclusion criteria	Funding sources and role of funder	Interventions (dose, duration)	Control	Baseline TSH	Number screened/ eligible/ enrolled	Number withdrawn/ analyzed
Biochemically euthyroid patients							
Michalopoulou 1998	Conditions and medications that affect lipid profiles		LT4 50	LT4 25 mg	stratified: 1.0 (mean) or ~2.6 (mean)	NR/NR/110	0/110
Pollack 2001	Current medical disorders	Association of Clinical Biochemists	LT4 100	Placebo	1.9 (mean)	NR/NR/25*	3/22*

Study, year	Outcomes assessed/ when assessed	How outcomes assessed (e.g., scales used)	LT4 vs. Placebo group results	Before/after results
Biochemically euthyroid patients				
Michalopoulou, 1998	Lipid profile		LDL reduced from 6.2 to 6.1 in 25 mg group and from 6.8 to 5.9 in 50 mg group	LDLc reduction was significant in 50 mg group
Pollack, 2001	Symptoms, vital signs, biochemical tests after 14 weeks	SF-36 plus validated cognitive/ memory testing	Among symptomatic patients (n=22), there were no important differences between LT4 and placebo groups in any SF-36, memory, or cognitive measures	Placebo significantly improved SF-36 general health and physical health scores

Study, year	Adverse effects assessed?	Adverse effects	Quality rating (good/fair/poor)	Relevance to screening	Comments	Questions
Biochemically euthyroid patients						
Michalopoulou, 1998	No		Poor	Fair-	Randomization was probably flawed, and blinding is not reported	
Pollack, 2001	Not assessed, except for SF-36 scores	In asymptomatic patients, LT4 sign. Reduced SF-36 vitality scores	Fair	N/A	Too small; authors note that it is only a "pilot study". Placebo effect, adverse effect of LT4 in healthy subjects, and baseline difference in cholesterol levels (6.3 vs. 5.2) between symptomatic and asymptomatic subjects deserve more study	