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Omega-3 Fatty Acids and Maternal and Child Health: An Update

Executive Summary

Introduction

The n-3 FA (including alpha linolenic acid [ALA], stearidonic acid [SDA], eicosapentaenoic acid [EPA], docosapentaenoic acid [DPA], and docosahexaenoic acid [DHA]) are a group of essential long-chain and very-long-chain polyunsaturated fatty acids (PUFA). Along with the n-6 FA (including linoleic acid [LA] and arachidonic acid [AA]), they are involved in the eicosanoid pathway and are incorporated into cell membranes. Eicosanoids (including AA, prostaglandins, thromboxanes, and leukotrienes) have wide ranges of physiologic effects and play a key role in inflammation regulation. ALA is the simplest n-3 FA from which all other n-3 FA are metabolically derived. ALA must come from the diet as it cannot be made by the body. ALA is found in plants, such as leafy green vegetables, nuts, and vegetable oils such as canola, soy, and flaxseed. SDA can be formed from ALA via Δ6 desaturase, the rate-limiting enzyme in the pathway. When SDA enters the metabolic pathway, it is rapidly converted to EPA. EPA can be converted to DPA and vice versa. The conversion rates from ALA to EPA or DHA are highly variable. Good sources of EPA and DHA in the diet include fish, other seafood, other marine sources (e.g., algae and phytoplankton), and organ meats.

A role for n-3 FAs in prenatal and postnatal growth and development and risk for certain chronic diseases has been suggested by a variety of evidence from prospective cohort studies and randomized controlled trials (RCTs). In 2002, the Institute of Medicine (IOM) considered the evidence inadequate to establish an estimated average requirement

Context and Purpose of Review

The value of perinatal omega-3 fatty acids (n-3 FA) supplementation or infant formula fortification remains controversial. This review updates prior Evidence Reports and examines the effects of n-3 FA on pregnancy outcomes and infant development. N-3 FAs include marine oils (predominantly eicosapentaenoic acid and docosahexaenoic acid) and alphalinolenic acid.

Key Messages

- Randomized controlled trials (RCTs) found n-3 FA supplementation slightly increased the length of gestation and birth weight but did not decrease the risk for preterm birth or low birth weight.
- RCTs found n-3 FA supplements did not change the risk for gestational hypertension, pre-eclampsia, and peripartum depression.
- RCTs found maternal or infant n-3 FA supplementation did not alter growth patterns (attainment of height or weight) of full-term or preterm infants.
- RCTs found maternal or infant n-3 FA supplementation did not consistently benefit visual, neurological, or cognitive development and did not alter the risk for autism spectrum disorders.
- RCTs and observational studies found no consistent effects of maternal or infant n-3 FA supplementation on risks for eczema, allergies, asthma, or other respiratory disorders.

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(EAR) for n-3 FAs.[1] Thus, in the absence of sufficient evidence, the IOM set only Adequate Intake values (AIs), based on current population intake in the apparent absence of deficiency symptoms.[a] The IOM set the following AIs for n-3 FA (ALA, whose primary dietary sources are plant foods and algae) for healthy pregnant women and children:

Pregnant women: 1.4 grams(g)/day (d) of ALA
Infants (≤12 months): 0.5 g/d of n-3 FAs
Children (1 to 3 years): 0.7g/d of ALA
Children (4 to 8 years): 0.9 g/d of ALA

In 2004, at the request of the National Institutes of Health's (NIH) Office of Dietary Supplements (ODS), three Evidence-based Practice Centers (EPCs) conducted 11 systematic reviews (SRs) of the evidence for the health effects of n-3 FAs. Included among these SRs was one that encompassed outcomes related to the health of pregnant women and their children.[2] Maternal outcomes included gestational length, the risk for preterm birth, birth weight, intrauterine growth retardation ([IUGR], small-for-gestational age [SGA], and low birth weight [LBW]); birth length, head circumference, pregnancy hypertension and preeclampsia. Child health outcomes included neurological development; visual function in the first year of life; and various indices of cognitive development. This review found insufficient evidence to draw definitive conclusions about the effects of n-3 FA on maternal or child outcomes. Since the original review, many new studies and a number of SRs have examined the role of n -3 FAs in these outcomes. In addition, recent studies have suggested a potential role for n-3FAs in some related outcomes, e.g., the development of attention and working memory.[3] Thus ODS requested an update to the original report.

Scope and Key Questions

Scope of the Review

The current systematic review has four aims: 1) to update the original review on the topic of the effects of n-3 FAs on maternal and child outcomes,[2] 2) to identify the literature for several additional outcomes of interest (see below) not included in the original review; 3) to include prospective observational studies that were excluded from the original report when two or more RCTs were identified for an outcome of interest; and 4) to use this new review to collect additional information such as baseline intakes of or exposures to n-3 FAs and associations between exposure dose and response that would enhance the usefulness of this report for policy and clinical applications. Therefore, it is of interest to systematically compare results across different exposure/intervention products and study types (e.g., interventional vs. prospective cohort studies), and to account for differences in background n-3 FA intake.

This update includes the addition of seven new outcomes: (maternal) ante- and postnatal depression, and pediatric attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), learning disabilities, atopic dermatitis, allergies, and respiratory disorders, specifically looking at the risk for (or prevention of) these conditions in otherwise healthy individuals and their offspring, rather than the efficacy of n-3 FA in treating affected individuals.

Key Questions

The Key Questions address both issues of efficacy (i.e., causal relationships from trials) as well as associations (i.e., prospective cohort study results and outcomes or risk factors from RCTs for which the randomization may not be applicable). Compared with the Key Questions from the 2005 report, they expand the scope of the review to include additional maternal and child outcomes, as noted above and described below (shown in bold face).

Key Question 1: Maternal Exposures

- What is the efficacy of maternal interventions involving—or association of maternal exposures to—n-3 FAs (EPA, DHA, EPA+DHA, DPA, ALA, SDA, or total n-3 FA) on the following:
  - o duration of gestation in women with or without a history of preterm birth (less than 37 weeks gestation),
  - o incidence of preeclampsia/eclampsia/ gestational hypertension in women with or without a history of preeclampsia/ eclampsia/ gestational hypertension
  - o Incidence of birth of small-for-gestational age human infants
  - o **Incidence of ante- and/or postnatal depression in women with or without a history of major depression or postpartum depression**
- What are the associations of maternal biomarkers of n-3 intake during pregnancy and the outcomes identified above?
- What are the effects of potential confounders or interacting factors (such as other nutrients or use of other supplements, or smoking status)?

[a]The use of an AI instead of an EAR indicates the need for more research to determine, with confidence, the mean and distribution of requirements for that nutrient; AIs are based on much less data and more scientific judgment than are EARs.

- How is the efficacy or association of n-3 FA on the outcomes of interest affected by the ratio of different n-3 FAs, as components of dietary supplements or biomarkers?
- How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on the outcomes of interest?
- Is there a threshold or dose-response relationship between n-3 FA exposures and the outcomes of interest or adverse events?
- How does the duration of the intervention or exposure influence the effect of n-3 FA on the outcomes of interest?

Key Question 2: Fetal/childhood exposures

- What is the influence of maternal intakes of n-3 fatty acids or the n-3 fatty acid content of maternal breast milk (with or without knowledge of maternal intake of n-3 FA) or n-3 FA-supplemented infant formula or intakes of n-3 FA from sources other than maternal breast milk or supplemented infant formula on the following outcomes in term or preterm human infants?
  - Growth patterns
  - Neurological development
  - Visual function
  - Cognitive development
  - **Autism**
  - **Learning disorders**
  - **ADHD**
  - **Atopic dermatitis**
  - **Allergies**
  - **Respiratory illness**
- What are the associations of the n-3 FA content or the n-6/n-3 FA ratio of maternal or fetal or child biomarkers with each of the outcomes identified above?

Key Question 3: Maternal or childhood adverse events:

- What are the short and long-term risks related to maternal intake of n-3 fatty acids during pregnancy or breastfeeding on
  - Pregnant women
  - Breastfeeding women
  - Term or preterm human infants at or after birth
- What are the short and long-term risks associated with intakes of n-3s by human infants (as maternal breast milk or infant formula supplemented with n-3 FA)?
- Are adverse events associated with specific sources or doses?

Methods

The present review evaluates the effects of—and the associations between—n-3 FAs intakes (including EPA, DHA, DPA, ALA, SDA, and n-3 biomarkers) and maternal and child health outcomes. The Evidence-based Practice Center (EPC) conducted the review based on a systematic review of the published scientific literature using established methods as outlined in the Agency for Healthcare Research and Quality (AHRQ)'s Methods Guide for Comparative Effectiveness Reviews.[4]

This review is conducted in parallel with a systematic review of n-3 FA and cardiovascular disease, conducted by another EPC. Several aspects of the reviews are being coordinated, including eligibility criteria regarding interventions and exposures, search strategies, structure of the reviews, and assessments of the studies' risk of bias, strength of the bodies of evidence, and abstraction of study characteristics needed to assess causality.

We convened a Technical Expert Panel (TEP) to help refine the research questions and protocol. We discussed the Key Questions, analytic framework, study eligibility criteria, literature search, and analysis plans. The protocol was entered into the PROSPERO register (registry number CRD42015020638).

Literature Search Strategy

We modified the existing search strategies from the original report (see Appendix A) to include a complete set of terms for the new outcomes of interest based on searches we have conducted on these topics for previous reviews and consultation with colleagues. We conducted literature searches in Medline (Pubmed), Embase, the Cochrane Collection, Web of Science and Centre for Agriculture and Biosciences (CAB). For the topics of depression; ADHD; autism; and cognitive, neurological, and visual function development, we searched PsychInfo. We did not search for unpublished (grey) literature; however a notice was published in the Federal Register requesting unpublished data from manufacturers of omega-3 fatty acid-fortified infant formulae and dietary supplements. Searches for all topics began with the year 2000. For the newly added topics, we "reference mined" articles that we identified to determine whether any studies conducted and published prior to 2000 should be obtained and included. Studies in the original report deemed eligible for pooling with newly identified studies were included, as were prospective cohort and nested case control studies excluded from the original report that met current inclusion criteria.

The search was updated upon submission of the draft report for peer and public review.

Inclusion and Exclusion Criteria

The eligibility criteria applied to the search results were mostly similar to the criteria used in the original (2005) review. The populations were expanded to accommodate the expanded outcomes of interest. The interventions and exposures remain the same as those in the original report, with the addition of two n-3 FA (DPA and SDA). Included study designs have also been modified slightly.

The Eligibility Criteria are outlined here according to the PICOT framework, with indications of the Key Questions to which they apply.

- Population(s):
  - Key Question (KQ) 1(Maternal exposures and outcomes)
    - Healthy pregnant women (for outcomes of birth weight, intrauterine growth restriction/ small for gestational age, duration of gestation, risk of pre-eclampsia, eclampsia, or pregnancy hypertension)
    - Pregnant women with a history of pre-eclampsia, eclampsia, or pregnancy hypertension (only for outcome of risk of pre-eclampsia, eclampsia, or pregnancy hypertension)
    - Pregnant women with a history of major depressive disorder or postpartum depression (only for the outcome of risk for peripartum depression)
  - Key Question 2 (In utero and postnatal (through the first year of life) exposures and outcomes)
    - Healthy preterm or full term infants of healthy women/mothers whose n-3 fatty acid exposures were monitored during pregnancy
    - Breastfed infants of healthy mothers whose n-3 fatty acid exposure was monitored and/or who participated in an n-3 fatty acid intervention during breastfeeding beginning at birth
    - Healthy preterm or full term infants with and without family history of respiratory conditions (for outcomes related to atopic dermatitis, allergy, respiratory conditions) of mothers whose n-3 exposures were monitored during pregnancy and/or breastfeeding
    - Healthy children or children with a family history of a respiratory disorder, a cognitive or visual development disorder, autism spectrum disorder, ADHD, or learning disabilities, age 0 to 18 years who participated in an n-3 fatty acid-supplemented infant formula intervention or an n-3 supplementation trial during infancy
  - Key Question 3 (Adverse events associated with n-3 interventions)
    - Healthy pregnant women or pregnant women in the other categories described above
    - Offspring of women enrolled in an n-3 fatty acid intervention during pregnancy
    - Offspring of women whose exposure to n-3 fatty acids was assessed during pregnancy
    - Children whose exposure to n-3 fatty acids (through breast milk, infant formula, or supplementation) was monitored during the first year of life
- Interventions/Exposures:
  - Interventions (KQ1, 2, 3 unless specified):
    - N-3 fatty acid supplements (e.g., EPA, DHA, ALA, singly or in combination;
    - N-3 fatty acid supplemented foods (e.g., eggs) with quantified n-3 FA content
    - High-dose pharmaceutical grade n-3 fatty acids, e.g., Omacor®, Ropufa®, MaxEPA®, Efamed, Res-Q®, Epagis, Almarin, Coromega, Lovaza®, Vascepa® (icosapent ethyl)
      - Exclude doses of more than 6g/d, except for trials that report adverse events
    - N-3 fatty acid fortified infant formulae (KQ2,3)
      - E.g., Enfamil® Lipil®; Gerber® Good Start DHA & ARA®; Similac® Advance®
      - N-3 FA fortified follow-up formulae
      - Exclude parenterally administered sources
    - Marine oils, including fish oil, cod liver oil, menhaden oil, and algal with quantified n-3 FA content
    - Algal or other marine sources (e.g., phytoplankton) of omega-3 fatty acids with quantified n-3 content
  - Exposures (KQ1,2)
    - Dietary n-3 fatty acids from foods if concentrations are quantified in food frequency questionnaires
    - Breast milk n-3 fatty acids (KQ2)
    - Biomarkers (EPA, DHA, ALA, DPA, SDA), including but not limited to the following:
      - Plasma fatty acids
      - Erythrocyte fatty acids

        - Adipocyte fatty acids.
- Comparators:
  - Inactive comparators:
    - Placebo (KQ1, 2, 3)
    - Non-fortified infant formula (KQ2)
  - Active comparators
    - Different n-3 sources
    - Different n-3 concentrations (KQ1, 2, 3)
    - Alternative n-3 fortified infant formulae (KQ2)
    - Soy-based infant formula (KQ2)
    - Diet with different level of Vitamin E exposure
- Outcomes:
  - Maternal outcomes (KQ1)
    - Blood pressure control
      - Incidence of gestational hypertension
      - Maternal blood pressure
      - Incidence of pre-eclampsia, eclampsia
    - Peripartum depression
      - Incidence of antepartum depression[5]
      - Incidence of postpartum depression, e.g.,
        - Edinburgh Postnatal Depression scale
        - Structured Clinical Interview (SCI)
    - Gestational length
      - Duration of gestation
      - Incidence of preterm birth
    - Birth weight
      - Mean birth weight
      - Incidence of low birth weight/small for gestational age
  - Pediatric Outcomes (KQ2)
    - Neurological/visual/cognitive development
      - Visual development, e.g.,
        - Visual evoked potential (VEP) acuity
        - Behavioral visual acuity testing
          - Teller's Acuity Card test and others
        - Electroretinography
      - Cognitive development, e.g.,
        - Bayley's Scale of Infant and Toddler Development Mental Development Index (MDI)
        - Griffith Mental Developmental Scale
        - Kauffman Assessment Battery for Children
        - Neonatal Behavioral Assessment
        - Wechsler Scales
        - MacArthur Communicative Development Inventory
        - Fagan Test of Infant Intelligence
        - Ages and Stages Questionnaire
        - Stanford-Binet IQ
      - Neurological development
        - Bayley's Scale of Infant and Toddler Development Psychomotor Development Index (PDI)
        - Electroencephalograms (EEGs) as measure of maturity
        - Neurological/movement impairment assessment
        - Active sleep, quiet sleep, sleep-wake transition, wakefulness
        - Nerve conduction test
        - Latency Auditory evoked potential
    - Risk for ADHD
      - Validated evaluation procedures
        - E.g., Wechsler Intelligence Scale for Children,
        - Behavioral rating scales, e.g., Connors, Vanderbilt, and Barkley scales
    - Risk for Autism spectrum disorders
      - Validated evaluation procedures
        - E.g., Modified Checklist of Autism in Toddlers
    - Risk for learning disabilities
      - Validated evaluation procedures
    - Risk for atopic dermatitis
    - Risk for allergies
      - Validated allergy assessment procedures, preferably challenge (skin prick test or validated blood tests accepted)
    - Incidence of respiratory disorders
      - Spirometry in children 5 and over (peak expiratory flow rate [PEFR] and forced expiratory volume in 1 second [FEV1])
  - Key Question 3: Adverse effects of intervention(s)
    - Incidence of specific adverse events reported in trials by study arm
- Timing:
  - Duration of intervention or follow-up
    - Key Question 1,3 (maternal interventions/ exposures):

        - Interventions implemented anytime during pregnancy but preferably during the first or second trimester
        - Follow-up duration is anytime during pregnancy (for maternal outcomes of pre/eclampsia or maternal hypertension); term (for outcomes related to birth weight, duration of pregnancy); or within the first 6 months postpartum (for the outcome of postpartum depression)
    - Key Question 2, 3 (infant exposures):
        - Interventions implemented within one month of birth or exposures measured within 1 month of birth
        - Follow-up duration is 0 to 18 years
- Settings:
    - Community-dwelling individuals seen by primary care physicians or obstetricians in private or academic medical practices (KQ1, 3)
    - Community dwelling children seen in outpatient health care or educational settings (KQ2, 3)

We limited the study designs of interest to RCTs of any size, and to prospective cohort studies and nested case control studies of sample size 250 or greater (cross-sectional, retrospective cohort, and case study designs were excluded; studies must have measured intake/exposure prior to outcome). Only peer-reviewed studies published in English language were included. Unpublished studies were not included.

Study Selection

The DistillerSR software package was used to manage the search outputs, screening, and data abstraction. Title/abstract screening was conducted in duplicate). All title selections were accepted without reconciliation for further full-text review. Second-level screening of full text articles was conducted by two reviewers and differences reconciled (the project leaders settle disagreements, if needed).

Data Extraction

Accepted studies underwent single abstraction of study-level data and risk-of-bias assessment in Distiller, with audit by an experienced reviewer. Outcome data were abstracted by a biostatistician and audited by an experienced reviewer. We re-extracted data from studies included in the original report that are to be included in new pooled analyses as needed.

Methodological Quality (Risk of Bias) Assessment of Individual Studies

We assessed the methodological quality of each study based on predefined criteria. Risk of bias among RCTs was assessed using the Cochrane Risk of Bias tool,[6] which evaluates risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias. Risk of bias among observational studies was assessed using questions relevant for prospective studies from the Newcastle-Ottawa tools.[7] Both tools were supplemented with nutrition-specific items in consultation with the TEP (e.g., those related to uncertainty of dietary assessment measurements and compliance).[8-10]

Data Synthesis/Analysis

We considered meta-analyses when there were at least three trials with similar intervention (i.e. DHA, DHA+EPA, DHA+AA), follow-up time (i.e. birth, 12 months of age), and population (i.e. pregnant women, term infants, preterm infants). For trials that had groups with the same intervention but with varying doses, we averaged the outcome across doses for the main analysis. Forest plots were provided for random effects meta-analysis. We used the Hartung-Knapp-Sidik-Jonkman method for our random effects meta-analysis.[11-13] It has been shown that the error rates from this method are more robust than the previously used DerSimonian and Laird method.[14] Heterogeneity was assessed using the I2 statistic.[15] All statistical analyses were performed in R 3.2.0.[16]

New trial results were added to original meta-analyses, when appropriate, based on similarity of participants, interventions (including doses), and outcomes.[4]

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes

The strength of evidence was assessed for each outcome and exposure type using the method outlined in the AHRQ Methods Guide,4 in which the body of evidence for each outcome is assessed based on the following dimensions: study limitations (risk of bias), reporting bias, consistency (within and across study designs), directness (of study outcome measures), and precision, as well as the number of studies by study design. Based on these assessments, we assigned a strength of evidence rating (i.e., insufficient, low, moderate, or high level of evidence). The data sources, basic study characteristics, and each strength-of-evidence dimensional rating were summarized in a "Summary of Evidence Reviewed" table detailing our reasoning for arriving at the overall strength of evidence rating.

Peer Review and Public Commentary

A draft version of this report was reviewed by a panel of expert reviewers, including representatives from the American Academy of Pediatrics and the American College of Obstetrics and Gynecology, and the general public. The reviewers included experts in prenatal and postnatal development and in the clinical effects of n-3FA and representatives of dietary supplement trade organizations. These experts were either directly invited by the EPC Program or offered comments through a public review process. Revisions of the draft were made, where appropriate, based on their comments. The draft and final versions of the report were also reviewed by AHRQ. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Results

For this systematic review, we identified 95 RCTs and 48 eligible prospective longitudinal studies and nested case-control studies that were eligible for inclusion based on the prespecified inclusion criteria. Most of the RCTs evaluated the effects of marine oil supplements on weight gain during pregnancy (risk for low birth weight) and length of gestation (risk for preterm birth) or the effects of DHA with or without arachidonic acid ([AA], an n-6 FA) as supplements or added to infant formulas on infant neural, visual, and cognitive development. Most observational studies assessed the association between the status of particular n-3 FA and developmental outcomes.

We summarize the results of our review below by the outcomes of interest (maternal outcomes, childhood outcomes, adverse events), and within each outcome, by the target population for the intervention (e.g., pregnant women, preterm infants, term infants) where relevant, and further by the intervention or exposure. Findings included in this summary are those for which evidence was determined to be sufficient to draw a conclusion. Findings for all interventions/exposures across all outcomes and time points are described in full in the main text and the conclusions and strength of evidence are provided in Appendix G.

Maternal Exposures and Outcomes

Length of Gestation and the Risk for Preterm Birth

The original report found inconsistent effects of prenatal maternal n-3 FA supplementation on length of gestation or the risk for preterm birth and a consistent finding of no effects of prenatal maternal supplementation with EPA+DHA among a large number of RCTs. The current report identified a moderate level of evidence that maternal supplementation of DHA or DHA-enriched fish oil may increase gestational length, and a low level of evidence that maternal supplementation with EPA+DHA-containing fish oils may not have significant effects on infants' gestational length compared with placebo.

For the current report, pooled analysis of 11 RCTs among healthy pregnant women found a significant increase in length of gestation among mothers who received algal DHA or DHA-enriched fish oil (weighted mean difference [WMD] +0.34 week [95% CI 0.02, 0.67]) compared to placebo. Pooled analysis of seven RCTs showed no significant effect of DHA or DHA-enriched fish oil on the risk for preterm birth.

Two RCTs in healthy pregnant women showed that maternal fish oil supplementation (EPA+DHA) had no significant effects on length of gestation, while one RCT in at-risk pregnant women found that maternal fish oil supplementation significantly increased the infants' mean gestational age compared with placebo. Pooled analysis of nine RCTs (in four publications) found no effects of EPA+DHA supplementation in pregnant women who were at risk for preterm birth on the incidence of preterm birth.

Random-effects meta-regression found no significant linear dose-response relationships between doses of DHA, EPA, or DHA to EPA ratio (beta coefficient [SE]=-0.04 [0.09], P=0.67, n=9) and the effect sizes.

Prospective studies are sparse and found no consistent associations of maternal exposures with outcomes related to length of gestation or preterm birth.

Birth Weight and the Risk for Low Birth Weight or Small-for- Gestational Age Birth

The original report did not find a significant effect of maternal n-3FA supplementation on the risk for low birth weight (LBW) or small-for-gestational age (SGA) birth or a clear association of any maternal biomarkers with risk for low birth weight or birth weight itself.

For the current report, we found a moderate level of evidence that maternal supplementation with DHA may increase birth weight and a low level of evidence that maternal supplementation with EPA+DHA may not have significant effects on birth weight compared with placebo. Pooled analysis of 12 RCTs showed significantly higher birth weights among infants (mixed term and preterm) whose mothers received algal DHA or DHA-enriched fish oil compared with placebo (WMD [95% CI]=90.12 [2.62-177.62] grams). Pooled analysis of five RCTs found no significant effect of maternal EPA+DHA supplementation

on infant birth weight. One RCT that assessed the effects of ALA on infant birth weight also showed no effects. These findings are consistent with prospective observational studies, which found that higher maternal blood DHA concentrations were associated with higher birth weight.

We also found a low level of evidence that maternal supplementation with EPA+DHA may not have significant effects on risk for delivering a LBW infant among healthy pregnant women. Pooled analysis of five RCTs showed no significant effects of fish or fish oil supplementation (doses ranged from 0.49 to 3 g/d) on birth weight compared with placebo or control (WMD [95% CI]=37.89 [-19.53, 95.31]) grams). Similarly, there is a low level of evidence that maternal n-3 FA supplementation may not have significant effects on the incidence of SGA. Two RCTs identified in our search found no effect of DHA alone or DHA-enriched fish oil on SGA outcomes in healthy pregnant women. Pooled analyses of four RCTs also found no significant effects of fish oil supplementation (DHA+EPA) on SGA/IUGR among women at increased risk for preterm delivery (OR [95% CI]=1.00, CI[0.70, 1.43]). Pooled analysis of four RCTs identified for the current review that assessed the effects of DHA alone or DHA-enriched fish oil showed no significant effects on the risk for delivering a LBW infant among women who were not at risk. Observational studies were sparse and showed mostly no associations between n-3FA intake or biomarkers and these outcomes.

Risk for Antenatal and Postnatal Depression

The outcome of risk for antenatal and postnatal depression was a new one for this review. Outcome measures for depression were heterogeneous so meta-analysis is not appropriate. Three RCTs that assessed the effects of prenatal supplementation with DHA alone, DHA+AA, or EPA-enriched fish oil or postnatal supplementation with DHA alone found no effects on risk of developing perinatal depression among healthy pregnant women. One small RCT showed that women who received prenatal DHA supplementation had significantly fewer symptoms of postpartum depression compared to the placebo group. Prospective studies mostly found no significant associations of maternal n-3 FA levels and risk of developing postnatal depression.

Risk for Gestational Hypertension or Preeclampsia

The original report found no consistent effect of maternal supplementation with n-3FA on the risk for gestational hypertension or preeclampsia.

For the current report, pooled analysis of three RCTs (one study identified for the current report and two studies from the original report) that randomized women not at high risk for poor pregnancy outcomes to DHA supplements or placebo showed no difference in the risk for gestational hypertension or preeclampsia among the DHA-treated women compared with the placebo-treated women (OR 0.94[0.66, 1.34], I2=0% (n=2,818); pooling studies of high-risk women who were randomized to fish oil or placebo also showed no effect (OR 1.04 [0.76 , 1.42], I2= 0%).

Childhood Outcomes

Postnatal Growth Patterns

The original report found no or inconsistent effects of maternal supplementation or infant formula fortification on postnatal growth patterns. The present review identified 24 additional RCTs and three observational studies that included pediatric growth pattern outcomes.

Seven RCTs and two observational studies that evaluated prenatal maternal n-3 FA interventions or exposures found no or mixed effects on growth patterns. Four RCTs examined a combination of prenatal and postnatal maternal n-3 FA interventions or exposures and found no or mixed effects on growth patterns. One RCT examined the effects of a postnatal maternal n-3 FA intervention and found higher body mass index (BMI) and head circumference in the intervention group at 2.5 years, but no effects were observed in an observational study of postnatal maternal exposures. Two RCTs examined a mixed set of postnatal maternal and postnatal infant n-3 FA interventions or exposures and found inconsistent effects of supplementation on growth. Six RCTs that assessed the effects of n-3 FA supplementation in infants on growth patterns were conducted among healthy infants or infants born to healthy women and found inconsistent associations with supplementation and growth patterns. Four RCTs conducted among preterm or LBW infants found inconsistent correlations of n-3 FA supplementation with growth pattern outcomes. Pooled analysis of four RCTs of prenatal (maternal) supplementation alone with DHA and EPA or fish oil (no postnatal supplementation) showed no significant effects on weight, length, or head circumference at 18 months. Pooled analysis of three studies of fortification of infant formula with DHA and AA also showed no effects on postnatal weight gain and length at 4 months among preterm infants.

Neurological Development

The original report found no consistent effect of maternal or infant supplementation with n-3 FA on neurological developmental outcomes and inconsistent associations with biomarkers.

Likewise, 17 RCTs identified for the current report found no consistent effects of n-3 FA alone or in combination with AA or linoleic acid (LA) on any of these outcomes compared with placebo. Two studies reported a positive effect of formula supplemented with DHA and AA on Bayley's Psychomotor Development Index (PDI) scores (an index of motor development) in preterm infants at 12 and 18 months, and two RCTs reported positive effects on brainstem maturation, but the remaining studies reported mixed effects on measures of motor development, including the PDI, in term infants supplemented with DHA and similarly mixed effects of DHA plus AA on other outcomes.

Visual Acuity

The original report found inconsistent effects of maternal and infant supplementation with n-3 FA on development of visual acuity, and differences between effects on behavioral measures of visual function and effects on electrophysiological measures (visual evoked potentials [VEP]).

Four RCTs that assessed the effects of prenatal maternal supplementation with DHA found no effects on infant visual acuity.

The current report identified one RCT that found that DHA supplementation of breast-feeding mothers resulted in improvement in one VEP outcome (transient VEP amplitude) at 4 and 8 months of age but not at 5 years of age; No differences were seen in other VEP measures, including sweep VEP and transient VEP latency, and no differences were seen using behavioral measures at any age.

Supplementation of preterm infants with any n-3 FA was assessed in nine RCTs identified for the original report and three RCTs identified for the current report. Pooling five studies that assessed VEP at 4 and 6 months showed insignificant effects of n-3 FA supplementation on VEP at 4 months (WMD -0.06 [-0.12, 0.01]; I2=1.7%) and 6 months corrected age (WMD -0.04[-0.09, 0.01] I2=0%).

Pooling studies that assessed supplementation of healthy term infants with formula containing any n-3 FA showed inconsistent effects on visual acuity. At two months follow-up, the pooled effect size for behavioral measurements was significant in favor of n-3 FA (WMD 0.07 [0.00, 0.14] six RCTs); the pooled effect size for VEP was insignificant (WMD 0.07[-0.03, 0.17], six RCTs). At 4 months follow-up, the pooled effect size for behavioral measurements was significant in favor of placebo treatment (WMD -0.05 [-0.08, -0.01], six RCTs); the pooled effect size for VEP was significant in favor of n-3 FA (WMD -0.10[-0.14, -0.07], eight RCTs). At 12 months follow-up, the pooled effect size for behavioral measures was insignificant (WMD -0.01[-0.04, 0.01]); the pooled effect size for VEP was significant in favor of n-3 FA (WMD -0.14 [-0.17, -0.12]).

Supplementation of healthy term infants with formula containing DHA+AA also showed inconsistent results. Eight studies identified for the original report showed no differences at 2, 4, 6, 8 and 9 months; however four studies that assessed VEP at 12 months showed a significant pooled effect size in favor of DHA+AA (p=0.01). Two new studies were identified for the current report that assessed the effect of supplementation with DHA+AA on VEP at 4 and 12 months. At 4 months, the pooled effect size for VEP was significant in favor of DHA+AA (WMD -0.10 [-0.14, -0.07], five RCTs). At 12 months follow-up, the pooled effect size for VEP was also significant in favor of DHA+AA (WMD -0.14 [-0.17, -0.12] six RCTs). None of the analyses showed evidence for publication bias.

A small number of trials assessed the association between maternal or infant biomarkers of n-3 FA status and subsequent visual acuity, with inconsistent findings.

Cognitive Development

The original report found inconsistent effects of n-3 FA supplementation on cognitive development. follow-up. We identified ten RCTs of pregnant women that reported cognitive outcomes in their offspring (including the only RCT identified in the original systematic review); only two reported significant results.

Six RCTs, including two from the original review, reported on supplementation for lactating women, including fish oil, cod liver oil, or high-DHA algal oil (two studies each); none reported significant results.

The original review included six RCTs in preterm infants that reported cognitive outcomes, while the current one identified an additional six reports on five RCTs. Seven RCTs of preterm infants reported the Bayley MDI score at 18 to 24 months of age; the pooled difference between the intervention and placebo groups was significant. The other RCTs reported mixed results.

Regarding healthy infants, the original review reported that six of eight RCTs did not find a significant difference between intervention and placebo groups in Bayley MDI scores. The current review identified five additional reports on four RCTs that measured cognitive outcomes. The pooled difference in MDI scores at 18 months was not significant when 3 RCTs were pooled. The RCTs that could not be pooled reported insignificant results regarding cognitive outcomes.

Among six observational studies identified for the current report, almost no associations between biomarker levels of n-3FAs and cognitive outcomes were noted. In one observational study that controlled for 18 potential confounders, low levels of AA in erythrocytes of pregnant women were associated with lower performance IQ; high levels of adrenic acid were associated with lower verbal IQ; and low levels of DHA were associated with lower verbal and full scale IQ at age 8; however, the authors caution that the effect sizes were small.

Risk for Autism, Learning Disorders, and Attention Deficit Hyperactivity Disorder

Developmental outcomes newly included for the current report were the risk for Autism Spectrum Disorders (ASD), Learning Disorders, and Attention Deficit Hyperactivity Disorder (ADHD). Long-term follow-up on one RCT of pregnant women and one RCT of preterm infants found no association between n-3 FA and reduced risk of ASD. One large observational study on ASD was identified; women with the highest quartile of total PUFA intake while pregnant were at lower risk of having a child with ASD than women in the lowest quartile (after controlling for many important potential confounders). The authors advised that the results should be interpreted with caution, given the small number of cases. Two RCTs of preterm infants and one RCT of pregnant women measured attention or reported diagnoses of ADHD at long-term follow-up; no association was found with earlier interventions or biomarker levels. No studies of other learning disorders were identified.

Allergy, Atopic Dermatitis, and Respiratory Conditions

Additional outcomes newly included in the current report were risks for atopic dermatitis/eczema, risks for allergies, and risks for respiratory illnesses, including asthma. A number of studies were conducted in mothers or infants at high familial risk for allergies or asthma.

Atopic dermatitis/eczema: Four prenatal and three postnatal RCTs showed inconsistent effects of maternal n-3 FA supplementation on the risk for atopic dermatitis/eczema: Only one of the prenatal studies found a significant reduction in eczema risk. Only one of seven prospective observational studies found higher concentrations of breast milk n-3 FA to be significantly associated with a lower risk of developing atopic dermatitis; the remaining six studies found no associations between n-3 FA exposures (measured through maternal dietary intake or breast milk composition) and risk for atopic dermatitis/eczema. Studies that assessed the association of biomarkers with this risk observed inconsistent associations of risk for atopic dermatitis with plasma levels of DHA, erythrocyte EPA, AA levels, and EPA/AA ratios. One of four prospective observational studies of n-3 FA biomarkers (in cord blood or maternal blood sample) found decreased risk of eczema and increasing AA levels, with the remaining three studies showing no effects.

Food allergies: Metaanalysis of three RCTs that assessed the effect of maternal supplementation with DHA plus EPA showed a reduction in the risk for food allergies that was not statistically significant. Use of infant formula fortified with DHA and AA or tuna oil or administration of fish oil capsules did not influence the risk for allergies. Prospective observational studies showed no consistent associations of maternal or infant n-3 FA exposures with risk for allergies.

Respiratory illness/asthma: Among 8 RCTs and follow-up studies that assessed the effect of prenatal n-3 FA supplementation on the risk for respiratory illnesses (including wheeze, asthma, persistent cough, inflammation, and respiratory infections), only two reported significant effects—decreases in the risk for asthma—but these effects were not consistent over time. A metaanalysis of three postnatal interventions that assessed the effects of DHA-supplemented formula on risk for wheeze found no significant effect. Prospective observational studies and biomarker studies reported inconsistent associations between various postnatal n-3 FA and n-6 FA exposures and risk for respiratory illnesses, with some studies showing an association between lower DHA, EPA, or total n-3 FA exposures or higher n-3 FA to n-6 FA ratios and lower risk for respiratory conditions (wheeze or asthma) but some studies of the same exposures showing no effects.

Adverse Events

The original report identified 21 RCTs that reported on adverse events with n-3 FA supplementation in pregnant women, breastfeeding mothers, and preterm and term infants. Overall they found that n-3 FA supplements and fortified formulas were well tolerated. Pregnant and breastfeeding women reported no serious adverse events, and adverse events in these groups were limited to mild GI symptoms. Among both preterm and term infants, adverse events were largely limited to GI symptoms also, with most serious adverse events attributable to morbidities associated with prematurity.

The current report identified 20 RCTs that reported on adverse events. The profile of both non-serious and serious adverse events in this report was identical to that of the original report. None of the observational studies identified for the current report described adverse events.

Discussion

Overall Summary and Strength of Evidence

As with the original report, most of the studies identified for the current report assessed the effects of n-3 FA interventions (or associations with exposures) on birth weight (or risk for low birth weight or intrauterine growth retardation), gestational length (or risk for preterm birth), and cognitive outcomes among children. Among studies reporting on the same outcomes, results were often inconsistent across studies.

The current study identified a small but statistically significant effect of DHA supplementation of pregnant women on the length of gestation, strengthening a non-statistically significant finding in the original report. As in the original report, the current report found no effect of DHA- or other n-3 FA supplementation on the risk for preterm birth, and observational studies provided inconsistent results. The difference in findings with respect to length of gestation (a continuous variable) and the risk for preterm birth (a dichotomous variable) may be attributable to any of several factors. Many more studies assessed length of gestation than assessed risk for preterm birth. The effect size for the increase in gestational length may not have been large enough to translate to an observable decrease in risk for preterm birth. Alternatively, the exclusion of preterm infants from some studies that assessed effects of supplementation on length of gestation could have skewed the results, or the populations enrolled in studies that assessed risk for preterm birth may have had sufficient baseline n-3 FA status. Too few studies assessed baseline status to examine this possibility.

The current study also found a significant effect of maternal DHA supplementation on birth weight in a pooled analysis of twelve studies, in contrast to the original report, which saw no effect from pooling two studies. Similar to the original report, a pooled analysis for the current report saw no significant effect of supplementation with DHA on the risk for low birth weight among women who were not at risk due to a prior low-birth-weight pregnancy. Reasons for the difference in these two outcomes may be similar to those posited for length of gestation. In addition, a study by Makrides and colleagues included in this review reported that the increase in birth weight that resulted from DHA supplementation was largely attributable to the increase in gestational age at birth.[17]

This review also identified no significant effects of n-3 FA supplementation of pregnant women on perinatal depression and gestational hypertension/preeclampsia.

The current report identified effects of supplementing formula with n-3 FA on visual acuity of preterm infants at 4 and 6 months corrected age that were not statistically significant but approached borderline significance. The report also found small, statistically significant effects of supplementing infant formula with n-3 FA, mainly DHA plus AA, on visual acuity development in term infants at 4 and 12 months but not at 2 months, when assessed using VEP. However, when behavioral measurements were used, an increase in visual acuity was observed in supplemented infants only at 2 months but not at 4 or 12 months.Thus the observed effects were inconsistent across time and assessment methods.

The current report identified a significant effect of supplementing infant formula with n-3 FA on indices of cognitive development among preterm infants at 18 and 24 months corrected age, but no differences were seen on longterm followup (8 to 10 years). No significant effects of supplementations were seen on cognitive development among term infants. The findings regarding the effects of n-3 FA supplementation on other childhood neurodevelopmental outcomes (e.g. psychomotor development, autism spectrum disorder, attention deficit hyperactivity disorder, and learning disorders) and respiratory outcomes (atopic dermatitis/eczema, allergy, and respiratory disorders) were either lacking in evidence or too inconsistent across studies as well as within studies at different follow-up time points to draw any high strength conclusions.

A random-effects meta-regression showed no dose-response effects for n-3 FA and birth weight. Too few studies assessed the effects of n-3 FA using similar populations and outcome measures to enable dose-response or threshold estimation for other outcomes.

Few studies stratified outcomes according to risk groups, so it was usually not possible to assess whether the effectiveness of omega-3 interventions depended on level of risk. In addition, no RCTs stratified outcomes by baseline n-3 FA status, so it is not possible to assess whether adequacy of n-3 FA status might account for differences in outcomes across (or lack of outcomes within) studies.

Table A summarizes the findings for which we identified a low, moderate, or high strength of evidence (SoE) for an effect or no effect of n-3 FA.

Table A. Conclusions with strength of evidence for an effect or lack of effect

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
Maternal outcomes				
Length of gestation	Healthy pregnant women: n-3 FA[d] supplementation	12 RCTs 4 observational studies	Moderate	RCTs: Increase in gestational length compared with placebo Meta-analysis of 12 RCTs in update: WMD 0.33 (95% CI 0.04, 0.62) weeks. Observational studies: No associations. Original report: mixed findings
Length of gestation	Healthy pregnant women: Algal DHA or DHA-enriched fish oil supplementation	11 RCTs 4 observational studies	Moderate	RCTs: Increase in gestational length compared with placebo Meta-analysis of 11 RCTs in update: WMD 0.34 (95% CI 0.02, 0.67) weeks Observational studies: No associations. Original report: mixed findings
Length of gestation	Healthy pregnant women: EPA+DHA fish oil supplementation	7 RCTs 4 observational studies	Low	RCTs: No significant effects on gestational length compared with placebo Observational studies: 3 of 4 found no association. Original report: no effects found[e]
Risk for preterm birth	Healthy pregnant women: Algal DHA or DHA-enriched fish oil supplementation	7 RCTs	Low	RCTs: No significant effects on the incidence of preterm birth compared with placebo Meta-analysis of 7 RCTs: OR 0.87 (95% CI 0.66, 1.15)
Risk for preterm birth	At-risk pregnant women: EPA+DHA fish oil supplementation	9 RCTs 2 observational studies	Low	RCTs:No significant effects on the incidence of preterm birth compared with placebo Meta-analysis of 9 RCTs: 0.86 (95% CI 0.65, 1.15) Observational studies showed mixed results.
Birth weight	Healthy pregnant women: n-3 FA* supplementation	16 RCTs 10 observational studies	Moderate	RCTs: Significant Increase in birth weight compared with placebo Meta-analysis of 16 RCTs in update: WMD 74.8 (95% CI 12.4, 137.17) grams. Observational studies of dietary intake, supplement use, and biomarkers generally showed positive associations with birth weight. Original report: Mixed findings

Table A. Conclusions with strength of evidence for an effect or lack of effect (continued)

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
Birth weight	Healthy pregnant women: Algal DHA or DHA-enriched fish oil supplementation	12 RCTs 3 observational studies	Moderate	RCTs: Significant Increase in birth weight compared with placebo Meta-analysis of 12 RCTs: WMD 90.12 (95% CI 2.62, 177.62) grams Observational studies showed associations between DHA intake and biomarkers and birth weight. Original report: mixed findings
Birth weight	Healthy pregnant women: EPA+DHA fish oil supplementation	5 RCTs 4 observational studies	Low	RCTs: No significant effects on birth weight compared with placebo Meta-analysis of 5 RCTs: WMD 37.89 (95% CI -19.53, 95.31) grams Observational studies showed mixed associations with birth weight. Original report: no effects
Low birth weight	Healthy pregnant women: Algal DHA or DHA-enriched fish oil supplementation	4 RCTs	Low	RCTs: No significant effects on risk of low birth weight compared with placebo Meta-analysis of 4 RCTs: OR 0.72 (95% CI 0.43, 1.11)
SGA/IUGR	At-risk pregnant women: EPA+DHA or fish oil supplementation	4 RCTs 2 observational studies	Low	RCTs: No significant effects on SGA/IUGR compared with placebo Observational studies: no consistent association with SGA Meta-analysis of 4 RCTs: OR 1.00 (95% CI 0.70, 1.43)
Gestational hypertension	Normal-risk pregnant women: DHA supplementation	3 RCTs	Low	RCTs: No significant effect on risk for gestational hypertension in normal risk women Meta-analysis of 3 RCTs OR 0.94 (95% CI 0.66, 1.34)
Gestational hypertension	High-risk pregnant women: Marine oil supplementation	3 RCTs	Moderate	RCTs: No significant effect on risk for gestational hypertension among high-risk women Meta-analysis of 3 RCTs OR 1.04 (95% CI 0.76 , 1.42)
Peripartum depression	Pregnant women: Prenatal DHA, DHA-rich fish oil, DHA+AA, EPA+DHA/fish oil, or any n-3 FA	4 RCTs 8 observational studies	Low	RCTs: Nosignificant effect on risk for peripartum depression across studies. Observational studies showed no associations with risk for depression.[e]

Table A. Conclusions with strength of evidence for an effect or lack of effect (continued)

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
Infant and child outcomes				
Postnatal growth patterns	Pregnant women: Fish oil or DHA+EPA supplementation	7 RCTs 2 observational studies	Moderate	RCTs: No significant effect on postnatal growth patterns among healthy term infants. Observational studies: Consistent with RCTs[e]
Postnatal growth patterns	Breastfeeding women: Supplementation with any n-3FA	6 RCTs 1 observational study	Low	RCTs: No significant effect on postnatal growth patterns Observational study: consistent with RCTs[e]
Postnatal growth patterns	Preterm or term infants: Feeding infant formula fortified with DHA+AA	47 RCTs	Low	RCTs: No significant effect on postnatal growth patternse
Visual acuity	Pregnant women: Supplementation with DHA-enriched fish oil	4 RCTs	Low	RCTs: No significant effect on development of visual acuity in infants.[e]
Visual acuity	Preterm infants: Feeding infant formula supplemented with any n-3 FA	5 RCTs	Low	VEP RCTs: No significant effect in preterm infants 4 months corrected age WMD -0.06 (−0.12; 0.01)
Visual acuity	Preterm infants: Feeding infant formula supplemented with any n-3 FA	5 RCTs	Low	VEP RCTs: No significant effect on development of visual acuity in preterm infants 6 months corrected age WMD -0.04 (-0.09, 0.01)
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	6 RCTs	Low	Behavioral measures RCTs: Significant effect at 2 months WMD 0.07 (0.00, 0.14) six RCTs
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	6 RCTs	Low	VEP RCTs: No significant effect at 2 months WMD 0.07[-0.03, 0.17], six RCTs
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	6 RCTs	Low	Behavioral measures RCTs: No significant effect at 4 months WMD -0.05 (-0.08, 0.01) six RCTs
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	6 RCTs	Moderate	VEP RCTs: Significant effect at 4 months WMD -0.10(-0.14, -0.07), six RCTs
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	8 RCTs	Low	Behavioral measures RCTs:No significant effect of n-3 FA at 12 months WMD -0.10 (-0.14, -0.07)

Table A. Conclusions with strength of evidence for an effect or lack of effect (continued)

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
Visual acuity	Term infants: Feeding infant formula supplemented with any n-3 FA	8 RCTs	Moderate	VEP RCTs: Significant effect of n-3 FA at 12 months WMD -0.14 (-0.17, -0.12)
Visual acuity	Term infants: Feeding DHA plus AA-fortified infant formula	7 RCTs	Low	VEP RCTs: Significant effect of DHA+AAat 4 months. WMD -0.10 (-0.14, -0.07)
Visual acuity	Term infants: Feeding DHA plus AA-fortified infant formula	6 RCTs	Moderate	VEP RCTs: Significant effect of DHA+AA at 12 months WMD -0.14 (-0.17, -0.12)
Neurological development	Pregnant women: Supplementation with any n-3 FA	17 RCTs 5 observational studies	Low	RCTs: No significant effects on measures of neurological development across studies (insufficient numbers of studies of any outcomes to pool) consistent with observational studies.[e]
Cognitive development	Pregnant women: Supplementation with DHA+EPA or DHA + AA	10 RCTs	Moderate	RCTs: No significant effects on cognitive development across studies[e]
Cognitive development	Preterm infants: Supplementation with any n-3 FA	11 RCTs	Moderate	RCTs: Significant increase in cognitive (MDI) scores WMD 2.24; (95% CI 0.05, 4.43)
Cognitive development	Term infants: Supplementation with DHA+ AA	12 RCTs	Low	RCTs: No significant effect on cognitive development at 18-24 months WMD 0.75, 95% CI -9.29, 10.79
Autism Spectrum Disorders (ASD)	Pregnant women or preterm infants: Supplementation with DHA	2 RCTs 1 observational study	Low	RCTs: No significant effect on risk for ASD; association shown for intake of n-3 FA in observational study[e]
ADHD	Pregnant women or preterm infants: Supplementation with DHA	3 RCTs	Low	RCTs: No significant effect on risk for ADHD[e]
Atopic dermatitis/ eczema	Pregnant women: Supplementation with any n-3 FA or exposures as assessed by biomarkers	4 RCTs	Low	RCTs: No significant (and inconsistent) effects on risk for atopic dermatitis/eczema

Table A. Conclusions with strength of evidence for an effect or lack of effect (continued)

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
Atopic dermatitis/ eczema	Breastfeeding women or infants: Supplementation of mothers or infants through formula fortification with any n-3 FA or exposure as assessed with biomarkers	3 RCTs 7 observational studies	Low	RCTs: No significant (and inconsistent) effects on risk for atopic dermatitis/eczema across RCTs, consistent with observational studies[e]
Allergies	Pregnant women: Supplementation with any n-3 FA or exposures as assessed by biomarkers	3 RCTs 4 observational studies (including 3 biomarker studies)	Low	RCTs: No significant effect on the risk for food allergy at 12 months OR 0.54 (95% CI 0.05, 6.2); Observational studies: no consistent association of biomarkers and risk for allergy
Allergies	Breastfeeding women or infants: Supplementation of mothers or infants through formula fortification with any n-3 FA or exposure as assessed by biomarkers	3 RCTs 2 observational studies	Low	RCTs: No significant effect on the risk for food or dust mite allergy and no association of breastmilk or infant biomarkers and risk for allergies across observational studies[e]
Asthma and other respiratory illnesses	Pregnant women: Supplementation with any n-3 FA	6 RCTs	Moderate	RCTs: No significant effect on the risk for asthma and other respiratory illnesses Meta-analysis of 3 RCTs OR 0.95 95% CI 0.77, 1.16
Asthma and other respiratory illnesses	Breastfeeding women or infants: Supplementation of mothers or infants through formula fortification with any n-3 FA	3 RCTs	Moderate	RCTs: No significant effect on the risk for asthma and other respiratory illnesses[e]
Asthma and other respiratory illnesses	Pregnant women or infants: Any n-3 FA exposures	10 observational studies	Low	Observational Studies: Inconsistent associations with risk for respiratory illnesses across studies.[e]
Asthma and other respiratory illnesses: Wheeze	Breastfeeding women or infants: Supplementation of mothers or infants through formula fortification with DHA	3 RCTs 5 observational studies 4 biomarkers studies	Low	RCTs: No significant effect on risk for wheeze at 12 months; meta-analysis of 3 RCTs: OR 1.06 (95% CI 0.73,1.54) Observational studies: showed Inconsistent associations with risk for wheeze across studies
Adverse events				
Maternal adverse events Non-serious	Pregnant or breastfeeding women: Supplementation with n-3 FA in the form of fish oil	9 RCTs	Moderate	RCTs: Increased risk for mild gastrointestinal symptoms but no other consistent non-serious adverse events.[e]

Table A. Conclusions with strength of evidence for an effect or lack of effect (continued)

Outcome	Intervention/Exposure	Study Design[a]	Strength of Evidence[b]	Conclusion[c]
Maternal adverse events serious	Pregnant or breastfeeding women: Supplementation with n-3 FA in the form of fish oil	4 RCTs	Moderate	RCTs: No significant difference in risk for serious adverse events.[e]
Infant adverse events non-serious	Healthy term infants or preterm infants: Supplementation with n-3 FA in the form of fish oil alone or added to infant formula	13 RCTs	Moderate	RCTs:Increased risk for mild gastrointestinal symptoms across studies but no other consistent non-serious adverse events.[e]
Infant adverse events serious	Healthy term infants: Supplementation with n-3 FA in the form of fish oil	6 RCTs	Moderate	RCTs:No significant difference in risk for serious adverse events.[e]
Infant adverse events serious	Preterm infants: Supplementation with n-3 FA in the form of fish oil	RCTs	Low	RCTs:No significant difference in risk for serious events associated with preterm birth.[e]

[a]Figures represent numbers of studies considered as evidence in drawing the conclusion;
[b]Strength of evidence (SoE) was assessed using a modification of the GRADE method; the assessments for each domain considered in assigning the overall SoE grade are provided in Appendix G for each outcome; RCT outcomes were compared with observational study outcomes, when available, to contribute to the "consistency" domain;
[c]Meta-analysis results are shown for all outcomes for which studies were pooled; remaining conclusions are based on trends across studies;
[d]Any n-3 FA refers to a pooled analysis of studies that employed any or unspecified n-3 FA;
[e]RCTs determined to be too heterogeneous to permit pooling.

AA = arachidonic acid; ALA = alpha linolenic acid; CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; IUGR = intrauterine growth retardation; n-3 FA = omega-3 fatty acid; OR odds ratio; RCT = randomized controlled trial; SGA = small for gestational age; VEP = visual evoked potentials; WMD = weighted mean difference

Limitations

Within each category of analysis (by outcome, target of intervention, n-3 FA, and study design), studies we identified for this review (like the studies included in the original review) diverged greatly with respect to the sources, doses, and durations of interventions; definitions or tests used to measure outcomes; and follow-up times. For outcomes such as visual, neurological, and cognitive development, by necessity, the tests used over time (in studies with multiple follow-ups) changed to match maturity level. As a result, it was challenging to identify groups of studies that were sufficiently similar to pool, even with studies from the original report. In addition, many RCTs employed and reported the results of numerous outcome measures, which were often internally inconsistent or showed no apparent pattern over time. The majority of studies did not find statistically significant findings. Although one of the charges for the current report was to include observational studies that were excluded from the original report when sufficient numbers of RCTs reported on similar outcomes, only a small number of observational studies that were excluded from the original report met the inclusion criteria for the current report, and the observational studies identified for the current report seldom assessed outcomes that were similar to those assessed in RCTs.

Overall, both RCTs and observational studies included in this review had numerous quality concerns that increased the risk for bias. Across RCTs, the most common risk-of-bias limitation was a lack of intention-to-treat analyses (54 percent of the included RCTs). Of included RCTs, 36 percent failed to describe allocation concealment

sufficiently to determine whether it was adequate (and many studies failed to describe recruitment methods). Blinding of study participants contributed only slightly to potential risk of bias because participants were usually infants or children and outcomes were usually clinically apparent or assessed in a clinical laboratory. Thirty-seven percent of RCTs were at risk of attrition bias due to overall dropout rates greater than 20 percent, although most studies reported similar dropout rates between groups. Although 87 percent of the included RCTs reported similar baseline demographic characteristics between groups, 57 percent did not report baseline n-3 FA intake or status. This omission is a critical concern because baseline n-3 FA status likely affects response to changes in n-3 FA intake.

Across observational studies, the most common risk of bias limitation was the lack of representativeness of the cohorts to the population of interest: 35 percent were judged to be select populations or only somewhat representative. In most cases, these populations were described as having high intakes of fish; in several cases, the populations were at high risk for the outcome of interest or another condition. Another reporting inadequacy related to the ranges and distribution of n-3 FA exposures. Of included observational studies, most of the n-3 FA dietary intake assessments included only dietary sources (not n-3 FA supplements). This issue does not affect the quality of biomarker data; however, so many different n-3 FA biomarkers were investigated across studies, that it was impossible to make comparisons. Another limitation of many of these studies was the inability or failure to control for potentially important confounding factors; this issue is magnified for long-term follow up studies.

Few studies reported adverse events, but among the 20 studies that did report adverse events, 60 percent did not predefine or prespecify adverse events to be queried, and none used a recognized categorization system to prespecify or sort categories or levels of intensity of adverse events reported. Only 35 percent reported an active mode of collection of adverse event information, and of the studies that reported serious adverse events (or lack thereof), most did not define "serious adverse event." Of additional concern, studies of preterm infants often comingled morbidities associated with prematurity (such as bronchopulmonary dysplasia and retinopathy of prematurity) and adverse events that might be associated with the intervention. Only one study that met inclusion criteria considered whether mercury exposure could account for the findings on the effects of fish oil intake, but the findings were equivocal.

The population profiles differed somewhat between RCTs and observational studies. Understandably, a number of the RCTs were conducted in women at risk for premature birth, gestational hypertension, a low birth weight infant, or women with a personal or family history of allergy or asthma. However, most observational studies examining the associations between dietary n-3 FA intake or biomarkers of n-3 FA intake and birth, respiratory, allergy, or developmental outcomes were conducted in generally healthy populations. Most RCTs were also small in size, although most reported doing power calculations. Observational studies that enrolled fewer than 250 were excluded by design.

Study interventions or measured exposures tended to be highly heterogeneous. Studies that labeled themselves as studies of DHA alone often included some amount of EPA as well as n-6 FA (usually AA). Fish oil studies did not always report the oil's concentration of n-3 and n-6 FA in addition to the one of interest. Few studies assessed the effects of EPA alone and only one study assessed the effects of ALA alone. Of most concern was the heterogeneity in the description of the n-3 and n-6 FA contents of infant formulas and the systematic lack of assessment of formula intake (realizing the difficulty of this measurement in human infants). Few trials compared n-3 FA dose, formulation (e.g., ratio of EPA to DHA), or source. No trial compared different n-3 to n-6 FA ratios of supplements or intake. None of the observational studies attempted to determine a threshold effect of any associations between n-3 FA and the outcome of interest. Some observational studies failed to report median or range data of n-3 FA levels within quantiles, confidence intervals (or equivalent) of association hazard ratios, or conducted only linear analyses across a full range of n-3 FA values. In addition, studies varied in the range of n-3 FA status (e.g., intake level) within each study. The applicability of many of the observational studies to the U.S. population may also be limited by the higher baseline intakes of fish and other n-3 FA-containing foods and supplements among the populations in these studies.

Among studies that assessed associations between biomarkers of n-3 FA status and an outcome of interest, so many different n-3 FA biomarkers were investigated, that it was impossible to make comparisons across studies.

As mentioned above, another limitation of many of the studies was the inability or failure to control for potentially confounding factors. Observational studies often corrected for a large number of potential confounders, but many important factors could not be or were not measured; this issue is magnified for long-term follow up studies of cognitive development, where environmental factors were seldom considered. RCTs that reported cognitive outcomes at long-term follow up also rarely controlled for

potential confounders, although they did report baseline data on characteristics such as SES and parent education, which were usually statistically similar among placebo and intervention groups.

For the outcomes related to infant and child development (except for growth patterns), tests used to measure most outcomes were numerous and heterogeneous across studies regardless of the study designs, and follow-up times varied widely. As a result, studies for a number of outcomes of interest could not be pooled, either with studies identified for the original report or with newly identified studies. In addition, the multiplicity of measures all but ensured that some outcome measure would produce a significant effect. Understandably, studies of cognitive, neurological, and visual acuity development with multiple follow-up points were required to use age/stage-appropriate outcome measures, but they seldom attempted to account for these changes in outcome measures.

The RCTs and observational studies also differed in a number of ways regarding interventions and exposures, making it difficult to compare outcomes across the two study designs. Of note, the doses of n-3 FA supplements in RCTs were often much higher than the highest intake reported for observational studies. Furthermore, not all observational studies explicitly included n-3 FA supplements in their assessment of intake, and almost none of the RCTs attempted to account for background fish or n-3 FA intake as an effect modifier.

For a very small number of RCTs where no significant differences in outcomes were observed between intervention and placebo treatments, posthoc analysis found an association between a biomarker of n-3 FA and the outcome of interest. This observation would seem to suggest that the apparent lack of effect of the intervention on the outcome of interest might be attributable to the participants having had adequate baseline n-3 FA status. However the number of studies that conducted these follow-up analyses was too small to draw definitive conclusions. Likewise, very few RCTs assessed or reported baseline dietary intakes of n-3 FA or biomarker status.

Finally, due to the significant heterogeneity across studies, the interpretation of overall meta-analysis results is limited. Only a small number of RCTs conducted dose response assessments (usually with poor results). For those reasons, we did not attempt to do dose-response meta-analysis of observational studies and performed only a small number of meta-regressions on dose-response across RCTs.

Future Research Recommendations

The design of future RCTs should attempt to determine whether particular populations or individuals are more likely to benefit from n-3 FA supplements or fortified formulas, e.g., individuals with relatively low baseline intakes of n-3 FA. Therefore, studies need to measure—and match intervention groups according to—baseline n-3 FA biomarker status (although the current report has not clearly revealed the most relevant biomarkers). Researchers need to reach consensus on standardized formulations and on reporting of concentrations for interventions. The results of this review should help guide these decisions.

Studies also need to ascertain whether n-3 FA are more effective in individuals at increased risk for particular conditions (such as low birth weight, preterm birth, gestational hypertension, or, for infants, risk for delayed visual acuity development or atopy).

Some recent evidence suggests that individuals' abilities to benefit from dietary supplementation with n-3 FA (or breastfeeding) is influenced by polymorphisms within the gene encoding FADs2, an enzyme involved in the desaturation of fatty acids to convert precursors to LCPUFAs such as DHA. If these findings are confirmed, future studies may need to perform genetic profiles on potential participants and to exclude those who are genetically incapable of responding to supplementation.

Finally, identifying the most promising and clinically relevant outcome measures will be important to expanding the strength of the evidence base for the effectiveness of supplemental n-3 FA for maternal and childhood outcomes. The findings of large cohort studies are still needed to assess the potential role of n-3 FA status in the risk for conditions such as autism spectrum disorder, learning disabilities, and ADHD; however, it may be necessary first to identify clear intermediate risk factors for these conditions, because the length of follow-up needed for diagnosis of the conditions themselves greatly increases the potential interference of other confounding factors.

Conclusions

Most studies identified for this report examined the effects of fish oil (or other combinations of DHA and EPA) supplements on pregnant or breastfeeding women or the effects of infant formula fortified with DHA plus arachidonic acid. With the exception of small effects on birth weight and length of gestation (confirming the findings of the original report), n-3 FA supplementation or fortification has no consistent evidence of effects on peripartum maternal or infant health outcomes. No effects of n-3 FA were seen on gestational hypertension,

peripartum depression, or postnatal growth. Apparent effects of n-3 FA supplementation were inconsistent across assessment methods and followup times for outcomes related to infant visual acuity and cognitive development and prevention of allergy and asthma. No association was seen between n-3 FA exposures and the risk for autism spectrum disorders. Evidence was insufficient to draw conclusions regarding effects of n-3 FA on or associations of n-3 FA exposures with ADHD and learning disabilities. Future RCTs need to assess standardized preparations of n-3 and n-6 FA, using a select group of clinically important outcomes, on populations with baseline n-3 FA intakes typical of those of most western populations.

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Full Report

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