Evidence-based Practice Center Systematic Review Protocol

Project Title: Omega-3 Fatty Acids and Maternal and Child Health

I. Background and Objectives for the Systematic Review

The omega (n)-3 FAs (e.g., alpha linolenic acid [ALA], eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], stearidonic acid [SDA], and docosapentaenoic acid [DPA]) are a group of long-chain and very long chain polyunsaturated fatty acids (PUFAs) that serve as precursors for bioactive compounds such as eicosanoids and are integral components of cell membranes. 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 (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.[*] The IOM set the following AIs for n-3 FA 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 the risk for pregnancy hypertension and preeclampsia. Child health outcomes included risk for preterm birth, intrauterine growth retardation (IUGR) (small-for-gestational age and low birth weight); birth weight, length, and head circumference; neurological development; visual function in the first year of life; and various indices of cognitive development. 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-3s in some related outcomes, e.g., the development of attention and working memory.[3]

The current systematic review has four aims: a) to update the original review on the topic of the effects of n-3 FAs on maternal and child outcomes,[2] b) to identify the literature for several additional outcomes of interest (see below) not included in the original review; c) 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 d) to use this new review to collect additional information that would enhance the usefulness of this report for policy and clinical applications.

[**] The use of an AI instead of an EAR indicates the need for more research to determine,

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.

The additional outcomes may present several challenges: a limited literature base; the need to rely largely, if not completely, on population-based cohort studies (RCTs are likely to be rare, and case-control studies are inadequate to address these issues); and the need to assess and distinguish the effects of potential maternal and postnatal exposures on postnatal outcomes.

Furthermore, there are ongoing concerns in the scientific community regarding systematic biases and random errors in the determination of n-3 FA intakes from dietary and supplement sources, using currently available assessment tools. The limitations of the current methods have been discussed elsewhere.[4, 5] To date, no alternate methods are available. Until "error-free" or "bias-free" methodologies are developed, it is crucial to evaluate the available data with the methodological quality and the limitations in mind. Nutrient biomarkers can provide an objective measure of dietary status. However, the correspondence between intake and biomarker concentration reflects not only recent intake but subsequent metabolism (e.g., elongation, desaturation, metabolism to bioactive compounds). Current biomarkers used to estimate n-3 polyunsaturated fatty acids intakes include ALA, EPA, SDA, and DHA, and are measured in adipose tissue, erythrocytes, plasma, or plasma phospholipids, placenta, and umbilical cord.[6, 7]Adipose tissue FAs are thought to reflect long-term intake, erythrocytes FAs are thought to reflect the previous 120-day intake, and plasma FAs are thought to reflect more immediate intake.[7]

The original systematic review did not reach strong scientific conclusions for many of the outcomes of interest, most likely related, at least in part, to the fact that some n-3 FA exposures were from fish and other marine sources, some were from dietary supplements, some were indirect (through breast milk), and many studies did not assess biomarkers.[2] In addition, for outcomes of interest for which RCTs were available, observational studies were not considered, whereas for outcomes for which RCTs were unavailable or could not be conducted, the authors relied on observational studies of varying design. Studies of different designs each have their own strengths and weakness that may result in differences in conclusions. For example, observational studies based on self-reported dietary assessments (e.g., food frequency questionnaires) may inaccurately estimate n-3 FA intake; RCTs of specific fish or other n-3 FA rich food may impose an artificial dietary pattern that might not be applicable to the general population; RCTs of supplements might not fully account for differences in background n-3 FA intake; studies using either study design may have subtle differences in eligibility criteria, e.g., length of follow-up period, or inclusion of ALA, EPA and DHA or only EPA and DHA, that significantly impacted the final conclusions. 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. Also of interest is a systematic evaluation of possible reasons for inconsistencies between observational and RCT findings: Tabulating causality-related study features such as the Bradford Hill criteria will permit the systematic evaluation of possible reasons for inconsistencies between observational and clinical study findings.[8]

The 2005 review screened 2,049 abstracts, of which 117 articles (describing 89 studies) were included. Of the 89 studies, 63 were RCTs and 26 were observational studies. This review will update the outcomes included in the previous review and will expand the scope to include additional maternal (risk for perinatal depression) and childhood (risk for ADHD, autism, learning disabilities, allergy, and respiratory conditions) outcomes.

II. The 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.

1. Maternal Exposures
   - What is the efficacy of maternal interventions involving—or association of maternal exposures to—n-3 FA (EPA, DHA, EPA+DHA [long-chain n-3 FA], DPA, ALA, SDA or total n-3 FA) on the following:
     - duration of gestation in women with or without a history of preterm birth (less than 37 weeks gestation),
     - incidence of preeclampsia/eclampsia/gestational hypertension in women with or without a history of preeclampsia/ eclampsia/ gestational hypertension
     - Incidence of birth of small-for-gestational age human infants
     - **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)?
   - 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?
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?

3. Maternal or childhood adverse events:
   - What are the short and long term risks related to maternal intake of n-3s 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?

*Several additional outcomes were added to the original key questions. They appear in bold.

III. Analytic Framework

To guide the assessment of studies that examine the association between n-3 FA intake/exposure and the maternal and childhood outcomes of interest, we have created two analytic frameworks that map the specific proposed linkages associating the populations of interest, the exposures, modifying factors, and outcomes of interest. The framework graphically presents the key components of the study questions presented in section II and further described in the Methods section, below.

1. Who are the participants (i.e., what is the population and setting of interest, including the diseases or conditions of interest)?
2. What are the interventions?
3. What are the outcomes of interest (intermediate and health outcomes)?
4. What study designs are of value?

Specifically, this analytic framework depicts the chain of logic that evidence must support to link the intervention (exposure to n-3 FA) to improved health outcomes.

Figure 1. Analytic Framework for n-3 fatty acids in maternal health
Populations of interest, Exposure, Outcomes, and Effect modifiers are described. Solid connecting arrows indicate associations and effects reviewed in this report.

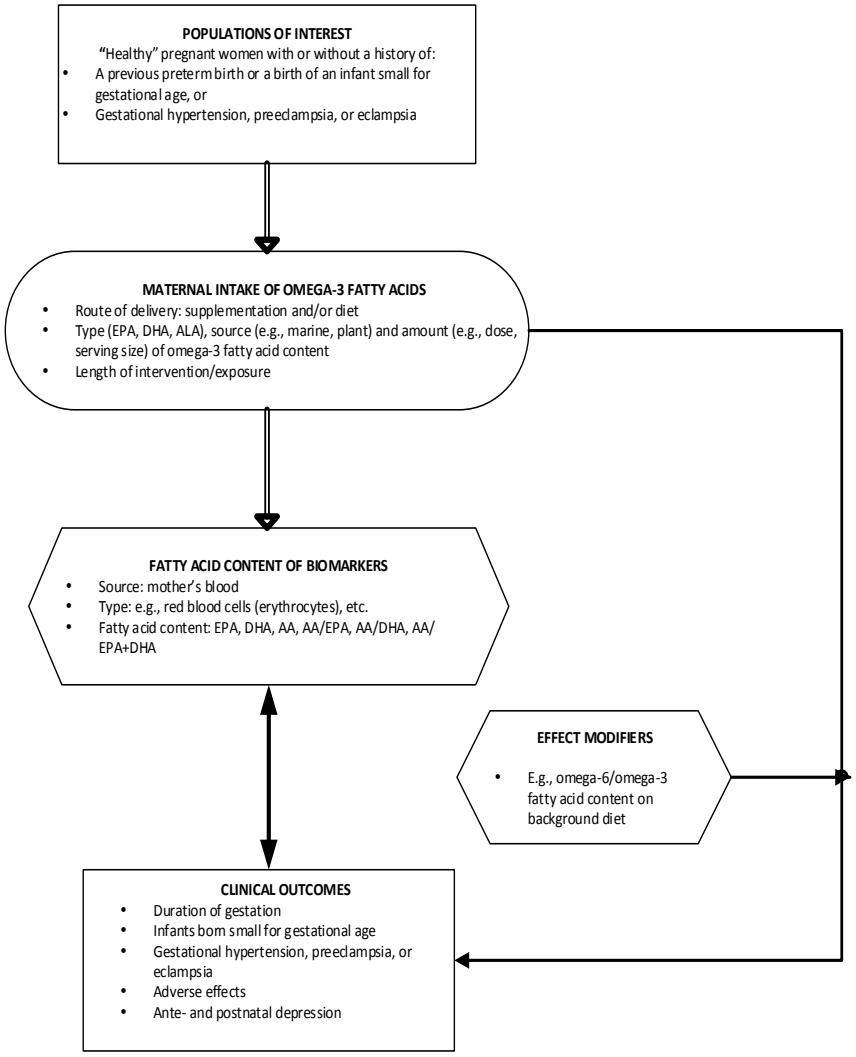
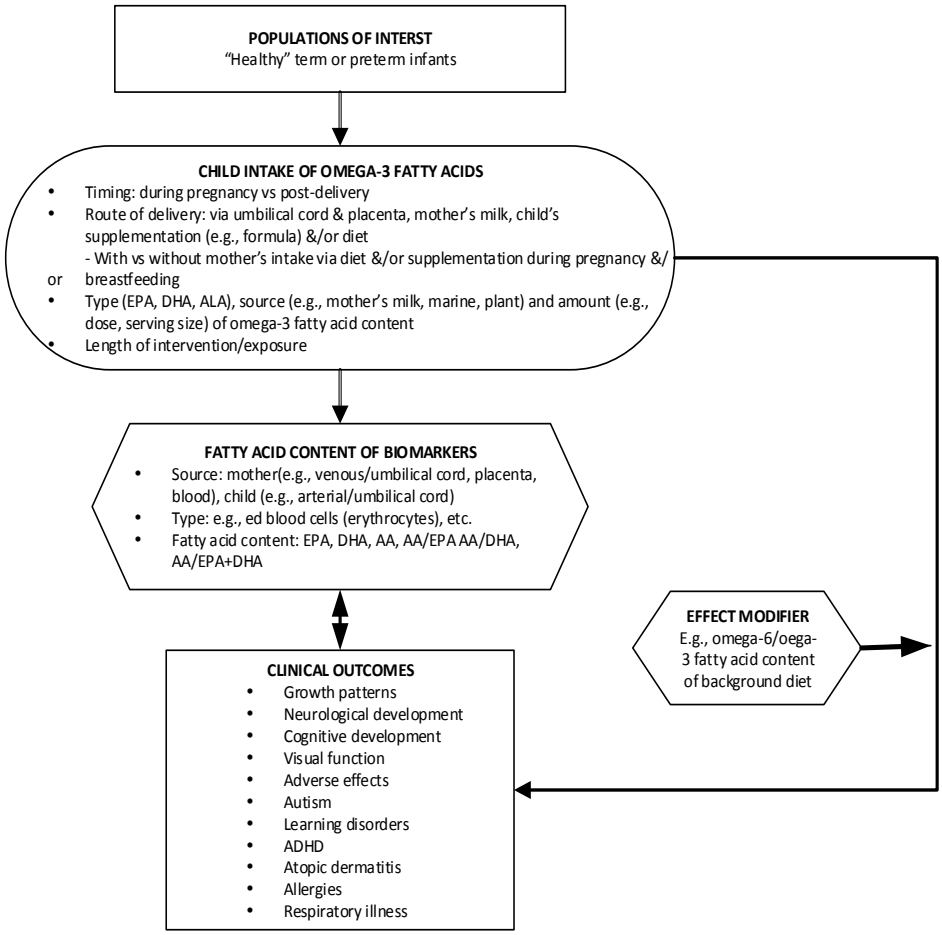


Figure 2. Analytic Framework for n-3 fatty acids in child health
Populations of interest, Exposure Outcomes, Effect modifiers were listed. Solid connecting arrows indicate associations and effects reviewed in this report.



IV. Methods

The current review evaluates the effects of—and the associations between--n-3 FAs (including EPA, DHA, DPA, ALA, SDA, and n-3 biomarkers) and maternal and child health outcomes. The Evidence-based Practice Center (EPC) will conduct 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.[9]

This review is being 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.

A. Criteria for Inclusion/ Exclusion of Studies in the Review

Inclusion and exclusion criteria are reviewed here, according to the PICOT framework. The proposed criteria are mostly similar to the criteria used in the original 2005 review. The populations are 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 been modified slightly.

The Eligibility Criteria are outlined here, 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 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 enriched infant formulae (KQ2,3)
      - E.g., Enfamil® Lipil®; Gerber® Good Start DHA & ARA®; Similac® Advance®
      - N-3 enriched follow-up formulae
      - Exclude parenterally administered sources
    - Marine oils, including fish oil, cod liver oil, and menhaden oil with quantified n-3 content
    - Algal or other marine sources 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 enriched 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[10]
      - 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 acuity
        - Visual acuity testing
          - Teller's Acuity Card test
        - Electroretinography
      - Cognitive/neurological development, e.g.,
        - EEGs as measure of maturity
        - Psychomotor developmental index from Bayley's scales
        - Bayley's mental development index
        - Knobloch, Passamanick, and Sherrard's developmental Screening Inventory scores
        - Neurological impairment assessment
        - Active sleep, quiet sleep, sleep-wake transition, wakefulness
        - Fagan Test of Infant Intelligence
        - Stanford-Binet IQ
        - Receptive Vocabulary
          - Peabody Picture Vocabulary Test-Revised
      - Auditory development
        - Nerve conduction test

        - Latency Auditory evoked potential
    - Risk for ADHD
        - Studies will be included only if they employ a validated evaluation procedure
            - E.g., Wechsler Intelligence Scale for Children,
            - Behavioral rating scales, e.g., Connors, Vanderbilt, and Barkley scales
    - Risk for Autism spectrum disorders
        - Studies will be included only if they employ a validated evaluation procedure
            - E.g., Modified Checklist of Autism in Toddlers
    - Risk for learning disabilities
        - Studies will be included only if they employ a validated evaluation procedure
    - Risk for atopic dermatitis
    - Risk for allergies
        - Studies will be included only if they employ a validated allergy assessment procedure, preferably challenge
    - Incidence of respiratory disorders
        - Spirometry in children 5 and over (peak expiratory flow rate [PEFR] and forced expiratory volume in 1 second [FEV_1])
- 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
            - Followup 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
            - Followup 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)

Study designs will be limited to RCTs, prospective cohort studies, and nested case control studies (cross-sectional, retrospective cohort, and case study designs will be excluded; studies must have measure of intake/exposure prior to outcome). Language will be restricted to English. Only peer-reviewed studies will be included; unpublished studies will not be included.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions

Prior to conducting our searches for the SR, we will obtain the studies included in the original report as well as prospective observational studies excluded from that report.[2]

While the protocol was being developed, we modified the existing search strategies from the original report (see Appendix) 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, and to reflect changes in search protocols.

Searches were designed and will be conducted in accordance with the latest edition of the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[9] Searches will be run in Medline (Pubmed), Embase, the Cochrane Collection, and Web of Science. For the topics of depression; ADHD; autism; and cognitive, neurological, and visual function development, we will run test searches in PsychInfo to assess whether we identify titles not identified in the other databases. We will run a test search CAB Health before determining whether to include this database. We will not search for unpublished (grey) literature; however a notice will be published in the Federal Register requesting unpublished data from manufacturers of omega-3 fatty acid-enriched infant formulae and dietary supplements. Searches for all topics will begin with the year 2000. For the newly added topics, we will "reference mine" articles that we identify to determine whether any studies conducted and published prior to 2000 should be obtained and included. Search results will be crosschecked with the list of studies included in the original report (as well as the list of prospective cohort studies excluded from the original report that must now be included) to ensure that no studies included in the original report are inadvertently included in the current report as "new" studies.

The DistillerSR software package will be used to manage the search outputs, screening, and data abstraction. Title/abstract screening will be conducted in duplicate (after a training session to ensure understanding of the inclusion and exclusion criteria and reasonable inter-rater reliability), using a screening form that lists the inclusion and exclusion criteria and allows selection of reasons for exclusion. All title selections will be accepted without reconciliation for further full-text review. Second-level screening of full text articles will be conducted by two reviewers and differences reconciled (the project leaders will settle disagreements, if needed). To focus on studies of the highest relevance and quality, additional exclusion criteria may be imposed for study size, exposure duration, or other similar criteria, if the number of studies identified is very large.

Accepted studies will undergo single abstraction of study-level data and risk-of-bias assessment in Distiller, with audit by an experienced reviewer. Outcome data will be abstracted by a biostatistician and audited by an experienced reviewer. We will re-extract

data from studies included in the original report that are to be included in new pooled analyses as needed. Reference lists of existing recent SRs on outcomes of interest will be reviewed to ascertain that we have not missed relevant studies. narrower than ours, we will conduct a bridge search to identify additional studies.[11]

C. Data Abstraction and Data Management

Data abstraction will follow the procedures described above. Data collection forms will be designed by the project team in Distiller SR, piloted by the reviewers, further modified, and then the final forms piloted with a random selection of included studies to ensure agreement of interpretation. Studies based on large prospective cohorts will be identified in their Distiller records to allow comparison to ensure data are not duplicated. Study-level data will include PICOTs, baseline nutritional status/ biomarkers/other evidence of initial exposure to n-3 fatty acids as well as status of other nutrients that could influence outcomes (e.g., vitamin E), method of exposure assessment and associated margin of error, inclusion/exclusion criteria, study design, comorbidities, other potential effect modifiers, analytic methods, and characteristics necessary to assess risk of bias, including recruitment, blinding, allocation concealment, description of completeness of final dataset, funding source, and other potential conflicts of interest.

Outcomes data, including clinical outcomes and intermediate outcomes (concentrations of biomarkers), will be abstracted in duplicate in Excel files by the biostatistician and one additional reviewer. At the end of the project, abstracted data will be uploaded to the Systematic Review Data Repository (SRDR) for full public accessibility.

D. Assessment of Methodological Risk of Bias of Individual Studies

We will assess the methodological quality of each study based on predefined criteria. Risk of bias among RCTs will be assessed using the Cochrane Risk of Bias tool,[12] 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 will be assessed using questions relevant for prospective studies from the Newcastle-Ottawa tools.[13] Both tools will be supplemented with nutrition-specific items in consultation with the TEP (e.g., those related to uncertainty of dietary assessment measurements and compliance).[14-16] Any quality issues pertinent to specific outcomes within a study will be noted and considered when determining the overall strength of evidence for conclusions related to those outcomes.

E. Data Synthesis

All included studies will be summarized narratively and in summary tables that show the important features of the study populations, design, intervention/exposure, outcomes, and results; we will build off and improve on the tables used in the original review. Separate summary tables may be used to describe studies that enroll particular subgroups of interest, studies that share a common exposure or intervention of interest, or studies that report on a particular outcome of interest, e.g., a particular test of visual acuity**.**

We will analyze the results of studies of different design separately, combining them if appropriate, and we will compare and contrast populations, exposures, and outcomes

across study designs, examining any differences in outcomes between interventional and observational studies.

New trial results will be added to original meta-analyses, when appropriate, based on similarity of participants, interventions (including doses), and outcomes.[9] When sufficient data are available and clinical heterogeneity is minimal, we will conduct dose-response meta-analysis (for observational studies) or meta-regression on doses (for RCTs) to support our qualitative synthesis. When new bodies of observational studies are added, possibility for random-effects multivariate dose-response meta-analysis will also be assessed.[17-21] The choice of fixed vs. random effects models for pooling results of RCTs will be based on our assessments of study outcome similarities.[12, 13] For meta-analysis of data with clear outliers, sensitivity analysis may be conducted, if appropriate to the question. If study designs permit, we will conduct network meta-analysis. Subgroup analyses will be explored within and across studies, based on the factors described in the key questions.

As valuable as dose-response data are, we will be very careful to avoid using data from different studies to infer dose-response unless evidence is clear that the study designs and conditions were highly homogeneous. Dose-response relationships will need to allow for threshold effects and curvilinearity; thus specialized approaches will be needed that allow the slope of the relationship to change above an apparent threshold that is not necessarily examined in the studies; these methods also need to consider adjusted analyses, use outcomes from all exposures in a study, allow for the grouping of data by study, and allow for different baseline risks by study and for between-study heterogeneity. Separate dose-response relationships will be analyzed for each combination of n-3 FA and biomarkers.

We will compile an appendix table with data related to possible causality criteria. Specifically, this table will list included studies with their population category (e.g., healthy pregnant women; women with a history of low birth weight, preterm birth, pre-eclampsia/gestational hypertension; women with a history of other potentially relevant conditions (e.g., obesity, gestational diabetes); healthy term infants), demographics; baseline n-3 intake, n-3 source, n-3 type, how n-3 intake measured; study design (e.g., RCT, prospective or retrospective longitudinal cohort, or other design); exposure timing and duration, followup duration, outcomes reported, effect sizes, difference in n-3 intake (between low and high intake groups), and a dose-corrected effect size.

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

The strength of evidence will be assessed for each outcome and exposure type using the method outlined in the AHRQ Methods Guide, 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 will assign 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 will be summarized in a "Summary of Evidence Reviewed" table detailing our reasoning for arriving at the overall strength of evidence rating (see the proposed table below). Applicability of studies to the populations and interventions that are the focus of the current review will be assessed also, as described below.

Table 1. Summary of Evidence Reviewed

Outcome Strength of Evidence Grade	Study Design (number of studies)	Study Limitations	Directness	Consistency	Precision	Reporting bias	Other Issues	Findings
Outcome 1 High, Moderate, Low, or Insufficient	RCTs: number Observational: number	Low, medium, or high	Direct or Indirect	Consistent or inconsistent	Precise or Imprecise	Undetected or Suspect	None or specific issue	Qualitative/ quantitative summary of findings

Characteristics of observational studies will be abstracted to enable assessment of Bradford-Hill Criteria, which are similar to the SOE criteria. The criteria and associated characteristics are listed in Table 2 below.

Table 2. Study Level Details Related to Causality

Study Author, year)	Dates	Location	Population	Sample size	Age	Sex	Race	Medical Hx	Risk type	Baseline n-3 intake	n-3 source	n-3 type(s)	Exposure timing	n-3 measure	Study design	Outcome	Reported Effect Size	Dose/intake	Dose-corrected ES	ROB Score

Table Note: ES effect size; ROB risk of bias

G. Assessing Applicability

The primary basis for assessment of applicability to healthy western populations will be the similarity of average intake of n-3 fatty acids (as fatty fish or other foods) to that of the U.S. at baseline. Studies of healthy pregnant women and healthy infants will have higher applicability than those enrolling women with a prior history of poor pregnancy outcomes or children with a family history of the conditions of interest. Studies in which the majority of participants were taking n-3 supplements at baseline will also be rated as having lower applicability.

V. References

1. Institute of Medicine of the National Academies. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids / Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board. Available at: http://www.nal.usda.gov/fnic/DRI/DRI_Energy/energy_full_report.pdf The National Academies Press. Washington, DC: 2005.

2. Lewin GA, Schachter HM, Yuen D, et al. Effects of omega-3 fatty acids on child and maternal health. Evidence report/technology assessment. 2005 Aug;(2005)(118):1-11.

3. Gould JF, Makrides M, Colombo J, et al. Randomized controlled trial of maternal omega-3 long-chain PUFA supplementation during pregnancy and early childhood development of attention, working memory, and inhibitory control. American Journal of Clinical Nutrition. 2014 Apr;99(4):851-9. PMID: 24522442.

4. Schoeller DA, Thomas D, Archer E, et al. Self-report-based estimates of energy intake offer an inadequate basis for scientific conclusions. Am J Clin Nutr. 2013 Jun;97(6):1413-5. PMID: 23689494.

5. Archer E, Hand GA, Blair SN. Validity of US Nutritional Surveillance: National Health and Nutrition Examination Survey Caloric Energy Intake Data, 1971-2010. Plos One. 2013 Oct 9;8(10)PMID: WOS:000325810900079.

6. Fekete K, Marosvolgyi T, Jakobik V, et al. Methods of assessment of n-3 long-chain polyunsaturated fatty acid status in humans: a systematic review. Am J Clin Nutr. 2009 Jun;89(6):2070S-84S. PMID: 19420097.

7. Serra-Majem L, Nissensohn M, Overby NC, et al. Dietary methods and biomarkers of omega 3 fatty acids: a systematic review. Br J Nutr. 2012 Jun;107 Suppl 2:S64-76. PMID: 22591904.

8. Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965 May;58:295-300. PMID: 14283879.

9. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.

10. American College of O, Gynecologists. Committee on Obstetric P. Committee opinion no. 453: Screening for depression during and after pregnancy. Obstet Gynecol. 2010 Feb;115(2 Pt 1):394-5. PMID: 20093921.

11. Integrating Bodies of Evidence: Existing Systematic Reviews and Primary Studies. Agency for Healthcare Research and Quality. Rockville, Maryland. In review.

12. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. PMID: 22008217.

13. Wells G, Shea B, O'Connell J, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. 2010. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed on May 5 2014.

14. Lichtenstein AH, Yetley EA, Lau J. Application of systematic review methodology to the field of nutrition. J Nutr. 2008 Dec;138(12):2297-306. PMID: 19022948.

15. Chung M, Balk EM, Ip S, et al. Reporting of systematic reviews of micronutrients and health: a critical appraisal. Am J Clin Nutr. 2009 Apr;89(4):1099-113. PMID: 19244363.

16. Newberry SJ, Chung M, Shekelle PG, et al. Vitamin D and Calcium: A Systematic Review of Health Outcomes (Update). Evidence Report/Technology Assessment No. 217. (Prepared by the Southern California Evidence-based Practice Center under Contract No. 290-2012-00006-I.) AHRQ Publication No. 14-E004-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2014.

17. Shekelle PG, Motala A, Johnsen B, et al. Assessment of a method to detect signals for updating systematic reviews. Syst Rev. 2014;3:13. PMID: 24529068.

18. Ahmadzai N, Newberry SJ, Maglione MA, et al. A surveillance system to assess the need for updating systematic reviews. Syst Rev. 2013;2:104. PMID: 24225065.

19. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992 Jun 1;135(11):1301-9. PMID: 1626547.

20. Orsini N, Li R, Wolk A, et al. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. Am J Epidemiol. 2012 Jan 1;175(1):66-73. PMID: 22135359.

21. Hamling J, Lee P, Weitkunat R, et al. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med. 2008 Mar 30;27(7):954-70. PMID: 17676579.

VI. Definition of Terms

If not applicable, simply make a note to that effect.

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Example table below:

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol	Specify where the change would be found in the protocol	Describe the language of the original protocol.	Describe the change in protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias.

VIII. Review of Key Questions

AHRQ posted the key questions on the Effective Health Care Website for public comment. The EPC refined and finalized the key questions after review of the public comments, and input from Key Informants and the Technical Expert Panel (TEP). This input is intended to ensure that the key questions are specific and relevant.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers all peer review comments on the draft report in preparation of the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published three months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. xxx-xxx from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Appendixes

Search Strategy

DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 1/1/2000-10/8/2014

LANGUAGE:
English

SEARCH STRATEGY:
#1 'body growth'/exp OR 'child development'/exp OR 'gestational age'/exp OR 'prematurity'/de OR 'low birth weight'/exp

#3 gestat* AND (age* OR durat* OR week*)

#4 premature* OR preterm OR 'pre term'

#5 infant* OR baby AND low AND (birthweight OR weight)

#8 newborn OR neonat*

#9 'retrolental fibroplasia'/de OR 'attention deficit disorder'/de OR 'atopic dermatitis'/de OR 'autism'/exp OR 'hypersensitivity'/exp

#10 retrolental AND fibroplas* OR retinopathy NEAR/2 prematurity OR (attention AND deficit AND disorder) OR adhd OR atopic NEAR/3 dermatitis OR autism OR autistic OR asperger* OR ados OR allerg*

#11 'intrauterine growth retardation'/exp OR 'prenatal development'/exp OR 'fetus'/exp OR 'preeclampsia'/de OR 'puerperal depression'/de

#12 (fetal OR fetus OR intrauterine) NEAR/3 (growth OR develop*)

#13 preeclamp* OR 'pre eclampsia'

#14 pregnan* NEAR/10 toxemi*

#15 gestation* OR pregnan* AND (hypertens* OR toxemi*)

#16 gestation* AND (child* OR newborn* OR infan* OR neonat* OR baby OR babies OR pediatr* OR paediatr*)

#17 depression NEAR/3 (postpartum OR postnatal OR 'post partum' OR 'post natal' OR antenatal OR 'ante natal')

#18 grow* NEAR/3 (child* OR infant* OR infancy)

#19 'visual disorder'/exp AND congenital

#20 congenital AND (vision OR visual) AND disorder*
#21 'learning disorder'/exp OR learning NEAR/3 disorder* OR dyslexi* OR discalculi*

#22 respiratory NEAR/3 illness OR respiratory NEAR/3 disease* OR respiratory NEAR/3 condition* OR asthma* OR wheez* OR respiratory AND syncytial AND virus

#23 infant* OR baby AND (premature* OR gestational) AND age

#24
#1 OR #3 OR #4 OR #5 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23

25 'icosapentaenoic acid'/exp

#26 'docosahexaenoic acid'/exp

#27 'omega 3 fatty acid'/exp

#28 'essential fatty acid'/exp

#29 'fish oil'/exp

#30 'omega 3' OR omega AND 3 OR omega3 OR polyunsaturated AND fat* OR pufa OR dha OR epa OR dpa OR long AND chain OR 'long chain'

#31 'docosapentaenoic acid'/exp OR 'docosapentaenoic acid' OR docosapent* OR docosahex* OR eicosapent* OR icosapent*

#32 n3 OR 'n 3' OR n AND 3 AND (oil* OR pufa OR fatty) AND acid*

#33 alpha AND linolenic OR alphalinolenic OR 'alpha linolenic'

#34 linolenate* OR cervonic OR timnodonic OR stearidonic

#35 menhaden NEAR/3 oil*

#36 flax* OR 'linseed'/exp OR linseed OR 'rape'/exp OR rape AND ('seed'/exp OR seed) OR 'rapeseed'/exp OR rapeseed OR 'canola'/exp OR canola OR soy OR soybean* OR 'walnut'/exp OR walnut OR 'mustard'/exp OR mustard AND ('seed'/exp OR seed) OR 'perilla'/exp OR perilla OR shiso NEAR/3 oil*

#37 walnut* OR butternut* OR soybean* OR 'pumpkin'/exp OR pumpkin AND ('seed'/exp OR seed) OR pumpkinseed*

#38 fish NEAR/2 oil*

#39 cod AND ('liver'/exp OR liver) AND oil* OR codliver AND oil* OR marine AND oil* OR marine AND fat

#40 'salmon'/exp OR salmon OR mackerel OR 'herring'/exp OR herring OR 'tuna'/exp OR tuna OR 'halibut'/exp OR halibut OR 'seaweed'/exp OR seaweed OR anchov* OR sardine*

#41 ropufa OR 'maxepa'/exp OR maxepa OR 'omacor'/exp OR omacor OR 'efamed'/exp OR efamed OR resq OR epagis OR almarin OR coromega OR 'lovaza'/exp OR lovaza OR 'vascepa'/exp OR vascepa OR 'icosapent'/exp OR icosapent AND ethyl

#42 fish NEAR/2 consum* OR fish NEAR/2 intake OR fish NEAR/2 diet*

#43 'mediterranean diet'/exp OR 'mediterranean diet'

#44 red AND ('blood'/exp OR blood) AND ('cell'/exp OR cell) OR 'phospholipid'/exp OR phospholipid OR 'plasma'/exp OR plasma AND fatty AND ('acid'/exp OR acid) OR 'plasma'/exp OR plasma OR 'phospholipid'/exp OR phospholipid OR 'triacylglycerol'/exp OR triacylglycerol OR cholesteryl OR 'ester'/exp OR ester OR adipos* OR fatty AND ('acid'/exp OR acid) OR 'erythrocyte'/exp OR erythrocyte OR ghost OR 'platelet'/exp OR platelet OR 'granulocyte'/exp OR granulocyte OR 'neutrophil'/exp OR neutrophil OR mononuclear OR 'ldl'/exp OR ldl OR 'hdl'/exp OR hdl AND (dha OR docosahexa?noic OR epa OR eicosapenta?noic OR sda OR stearidonic OR 'omega'/exp OR omega)

#45 #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44

#46 #25 OR #26 OR #27 OR #28

#47 #45 OR #46

#48 #24 AND #47

#49 #48 AND [humans]/lim AND [english]/lim AND [2000-2014]/py

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
MEDLINE ON OVID – 1/1/2000-10/10/2014

LANGUAGE:
English

SEARCH STRATEGY:
1 exp Growth/

2 exp Child Development/

3 exp Gestational Age/

4 Infant, Premature/

5 Infant, Low Birth Weight/

6 (gestat* and (age* or durat* or week*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

7 (prematur* or preterm or pre-term).mp.

8 ((Infant$ or baby) adj3 (low adj3 (birthweight or weight))).mp.

9 ((Infant$ or baby or birth) adj3 (prematur$ or gestational age)).mp.

10 (newborn or neonatal).mp.

11 1 or 2 or 3 or 4 or 5

12 6 or 7 or 8 or 9 or 10

13 11 or 12

14 Retinopathy of Prematurity/

15 retrolental fibroplasia$.mp.

16 Retinopathy of Prematurity.tw.

17 Attention Deficit Disorder with Hyperactivity/ or ADHD.mp. or attention deficit disorder*.mp.

18 Dermatitis, Atopic/ or (atopic adj3 dermatitis).mp.

19 (autism or autistic).mp. or Autistic Disorder/ or asperger*.mp. or Asperger Syndrome/

20 ados.mp.

21 Hypersensitivity/ or allerg*.mp.

22 14 or 15 or 16

23 Fetal Growth Retardation/

24 exp Embryo/ and Fetal Development/

25 exp Fetus/

26 ((fetal or fetus or intrauterine) adj3 (growth or develop$)).mp.

27 Pre-Eclampsia/

28 (Preeclamp$ or pre-eclamp*).mp.

29 (Pregnan$ adj10 Toxemia$).mp.

30 ((gestation$ or pregnan$) and (hypertens$ or toxemia$)).mp.

31 (gestat$ and (child$ or newborn$ or infan$ or neonat$ or baby or babies or pediatr$ or paediatr$)).mp.

32 Depression, Postpartum/ or (depression adj3 (postpartum or postnatal or post-partum or post-natal or post partum or post natal or ante-natal or antenatal or ante natal)).mp.

33
23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34 (grow* adj3 (child* or infant* or infancy)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

35 limit 34 to english language

36 congenital.mp. and (Vision Disorders/ or (vision adj3 disorder*).mp.)

37 limit 36 to english language

38 Learning Disorders/ or (learning adj3 disorder*).mp. or dyslexi*.mp. or discalculi*.mp.

39 limit 38 to english language

40 ((respiratory adj3 illness) or asthma* or wheez* or respiratory syncitial virus).mp.

41 limit 40 to english language

42
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 35 or 37 or 39 or 41

43 limit 42 to (english language and yr="2000 - 2014")

44 exp fatty acids, omega-3/

45 fatty acids, essential/

46 linolenic acids/

47 exp fish oils/

48 (omega 3 or omega-3 or omega3).mp.

49 (polyunsaturated fat$ or pufa or dha or epa or long chain or longchain).mp.

50 Docosapenta?noic.mp.

51 DPA.mp.

52 ((omega-3 or omega 3 or omega3) and fatty acid$).mp.

53 ((n 3 or n3 or n-3) and (oil$ or pufa or fatty acid$ or omega 3)).mp.

54 Docosahexaenoic Acids/

55 docosahexa?noic.mp.

56 Eicosapentaenoic Acid/

57 eicosapenta?noic.mp.

58 icosapent?enoic.mp.

59 (alpha linolenic or alphalinolenic or alpha-linolenic).mp.

60 (linolenate or cervonic or timnodonic or stearidonic).mp.

61 menhaden oil$.mp.

62 ((flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or perilla or shiso) adj2 oil$).mp.

63 (walnut$ or butternut$ or soybean$ or pumpkin seed$).mp.

64 (fish adj2 oil$).mp.

65 (cod liver oil$ or codliver oil$ or marine oil$ or marine fat$).mp.

66 (salmon or mackerel or herring or tuna or halibut or seaweed or anchov$ or sardine$).mp.

67 (Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl).mp.

68 (fish consumption or fish intake or (fish adj2 diet$)).mp.

69 (mediterranean adj diet$).mp.

70 ((red blood cell or phospholipid or plasma fatty acid or plasma or phospholipid or triacylglycerol or cholesteryl or ester or adipos$ or fatty acid or erythrocyte or ghost or platelet or granulocyte or neutrophil or mononuclear or LDL or HDL) and (DHA or docosahexa?noic or EPA or eicosapenta?noic or SDA or stearidonic or omega)).mp.

82
44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70

83
43 and 82

84 (randomized controlled trial or clinical trial or controlled clinical trial or evaluation studies or multicenter study).pt.

85 (exp clinical trial/ or evaluation studies or follow-up studies or prospective studies or exp randomized controlled trials/ or exp Randomized Controlled Trials as Topic/).sh.

86 (exp random allocation/ or exp double-blind method/ or exp single-blind method/).sh.

87 (exp placebos/ or exp longitudinal studies/ or exp cohort studies/).sh.

88 "prospective studies".af.

89 "prospective study".af.

90 evaluation studies.sh.

91 Cross-Sectional Studies.sh.

92 (clin$ adj trial$).af.

93 ((evaluation adj3 study) or (evaluation adj3 studies)).af.

94 (followup or follow-up or (follow$ adj2 up)).af.

95 (follow-up or followup or (follow$ adj2 up)).af.

96 (follow-up or "follow up" or (follow$ adj2 up)).af.

97 (follow-up or "follow up").af.

98 ("following up" or "followed up").af.

99 ((prospective adj3 study) or (prospective adj3 studies)).af.

100 (prospective adj3 observational).af.

101 (multicenter or multi-center).af.

102 (random$ or rct$).af.

103 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).af.

104 (placebo$ or comparative study or longitudinal or cohort* or observational or cross section$ or cross-section$ or food frequency questionnaire$).af.

105
84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 99 or 100 or 101 or 102 or 103 or 104

106 "before-and-after".af.

107 ((before adj2 after) or single-arm or "single arm").af.

108 (single-arm or "single arm").af.

109 "before and after".af.

110 "before-and-after".af.

111 105 or 106 or 107 or 108

112 83 and 111

113 (single-arm or "single arm").af.

114 "before and after".af.

115 "before-and-after".af.

116 110 or 111 or 112 or 113

117 88 and 116

118 case control.af.

119 88 and 118

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
COCHRANE DATABASES (Cochrane Reviews, Other Reviews, Trials, Methods Studies, Technology Assessments, Economic Evaluations) – 1/1/2000-10/23/2014

SEARCH STRATEGY:

#1 omega 3 or omega-3 or omega3:ti,ab,kw (Word variations have been searched)

#2 polyunsaturated or pufa or dha or epa or "long chain" or long-chain or longchain:ti,ab,kw

#3 Docosapentanoic or docosapentaenoic or docosahexanoic or docosahexaenoic or dpa or dha:ti,ab,kw

#4 icosapentanoic or eicosapentaenoic or icosapent*:ti,ab,kw

#5 (fatty acid or fatty acids*) and essential:ti,ab,kw

#6 "fish oil" or "fish oils" or linolenic or alpha-linolenic:ti,ab,kw

#7 alphalinolenic or alpha-linolenic:ti,ab,kw

#8 linolenate or cervonic or timnodonic or stearidonic:ti,ab,

#9 (n 3 or n3 or n-3) and (oil or oils or pufa or fatty acid or fatty acids):ti,ab,kw

#10 (menhaden or flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or perilla or shiso) and (oil or oils):ti,ab,kw

#11 walnut* or butternut*or soybean* or "pumpkin seed" or pumpkinseed*:ti,ab,kw

#12 "cod liver oil" or "codliver oil" or "marine oil" or "marine oils" or "marine fat":ti,ab,kw

#13 salmon or mackerel or herring or tuna or halibut or seaweed or anchov* or sardine*:ti,ab,kw

#14 Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl:ti,ab,kw

#15 (fish near/3 consum*) or (fish near/3 intake) or (fish near/3 diet*):ti,ab,kw

#16 mediterranean near/3 diet*:ti,ab,kw

#17 (red blood cell or phospholipid or plasma fatty acid or plasma or phospholipid or triacylglycerol or cholesteryl or ester or adipos* or fatty acid or erythrocyte or ghost or platelet or granulocyte or neutrophil or mononuclear or LDL or HDL) and (EPA or SDA or stearidonic or omega):ti,ab,kw

#18
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17

#19 growth or (child* next/3 development) or gestational age or premature infant or low birth weight:ti,ab,kw

#20 gestat* and (age* or durat* or week*):ti,ab,kw

#21 prematur* or preterm or pre-term:ti,ab,kw

#22 low near/3 (birthweight or weight):ti,ab,kw

#23 newborn or neonat*:ti,ab,kw

#24 Retinopathy near/3 Prematurity:ti,ab,kw

#25 retrolental fibroplasia*:ti,ab,kw

#26 ADHD or attention deficit disorder*:ti,ab,kw

#27 atopic near/3 dermatitis:ti,ab,kw

#28 autism or autistic or asperger*:ti,ab,kw

#29 ados or hypersensitiv* or allerg*:ti,ab,kw

#30 Fetal and growth and retard*:ti,ab,kw

#31 Embryo* and Fetal Development:ti,ab,kw

#32 Fetus or ((fetal or fetus or intrauterine) and (growth or develop*)):ti,ab,kw

#33 (Preeclamp* or pre-eclamp*) or (Pregnan* and Toxemi*):ti,ab,kw

#34 (Gestation* or pregnan*) and (hypertens* or toxemi*):ti,ab,kw

#35 gestat* and (child*or newborn* or infan* or neonat*or baby or babies or pediatr* or paediatr*):ti,ab,kw

#36 depression and (postpartum or postnatal or post-partum or post-natal or post partum or post natal or ante-natal or antenatal or ante natal):ti,ab,kw

#37 grow* near/3 (child* or infant* or infancy):ti,ab,kw

#38 congenital and (vision near/3 disorder*):ti,ab,kw

#39 (learning near/3 disorder*) or dyslexi*or discalculi*:ti,ab,kw

#40 (respiratory near/3 illness) or asthma* or wheez* or respiratory syncitial virus:ti,ab,kw

#41
#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40

#42
#18 and #41

#43
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17

#44
#19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40

#45
#43 and #44

#46 MeSH descriptor: [Growth] explode all trees

#47 MeSH descriptor: [Child Development] explode all trees

#48 MeSH descriptor: [Gestational Age] explode all trees

#49 MeSH descriptor: [Infant, Premature] explode all trees

#50 MeSH descriptor: [Infant, Low Birth Weight] explode all trees

#51 MeSH descriptor: [Retinopathy of Prematurity] explode all trees

#52 MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] explode all trees

#53 MeSH descriptor: [Dermatitis, Atopic] explode all trees

#54 MeSH descriptor: [Autistic Disorder] explode all trees

#55 MeSH descriptor: [Hypersensitivity] explode all trees

#56 MeSH descriptor: [Fetal Growth Retardation] explode all trees

#57 MeSH descriptor: [Embryonic and Fetal Development] explode all trees

#58 MeSH descriptor: [Fetus] explode all trees

#59 MeSH descriptor: [Pre-Eclampsia] explode all trees

#60 MeSH descriptor: [Depression, Postpartum] explode all trees

#61 MeSH descriptor: [Vision Disorders] explode all trees

#62 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees

#63 MeSH descriptor: [Fatty Acids, Essential] explode all trees

#64 MeSH descriptor: [Linolenic Acids] explode all trees

#65 MeSH descriptor: [Fish Oils] explode all trees

#66 MeSH descriptor: [Docosahexaenoic Acids] explode all trees

#67 MeSH descriptor: [Eicosapentaenoic Acid] explode all trees

#68
#46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61

#69
#62 or #63 or #64 or #65 or #66 or #67

#70
#68 or #41

#71
#69 or #44

#72
#70 and #71

#73
#69 or #18

#74
#70 and #73

#75
#74 not #45

==========

DATABASES SEARCHED & TIME PERIOD COVERED:
WEB OF SCIENCE – 11/1/2000-10/29/2014
SCOPUS – 11/1/2000-10/29/2014

FORWARD SEARCH ON THE FOLLOWING ARTICLE:
Alpha linolenic acid in cholesterol esters: a marker of alphalinolenic acid intake in newborns.
Babin F, Rodriguez A, Sarda P, Vandeputte B, Mendy F, Descomps B.
Eur J Clin Nutr. 2000 Nov;54(11):840-3.
PMID: 11114678

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
PUBMED – 1/1/2000-10/29/2014

RELATED ARTICLES SEARCH ON BABIN 2000 ARTICLE

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
PSYCINFO – 1/1/2000-10/30/2014

LANGUAGE:
English

OTHER LIMITERS:
POPULATION GROUP - Human

SEARCH STRATEGY:
Search modes - Find all search terms (FOR ALL SETS)

S1 omega 3 or omega-3 or omega3 OR polyunsaturated or pufa or dha or epa or "long chain" or long-chain or longchain OR Docosapentanoic or docosapentaenoic or docosahexanoic or docosahexaenoic or dpa or dha OR eicosapentanoic or eicosapentaenoic or icosapent*

S2 ((fatty acid or fatty acids*) and essential) OR "fish oil" or "fish oils" or linolenic or alpha-linolenic OR alphalinolenic or alpha-linolenic OR linolenate or cervonic or timnodonic or stearidonic

S3 ((n 3 or n3 or n-3) and (oil or oils or pufa or fatty acid or fatty acids)) OR ((menhaden or flax or flaxseed or flax seed or linseed or rape seed or rapeseed or canola or soy or soybean or walnut or mustard seed or perilla or shiso) and (oil or oils)) OR walnut* or butternut*or soybean* or "pumpkin seed" or pumpkinseed* OR "cod liver oil" or "codliver oil" or "marine oil" or "marine oils" or "marine fat"

S4 salmon or mackerel or herring or tuna or halibut or seaweed or anchov* or sardine* OR Ropufa or MaxEPA or Omacor or Efamed or ResQ or Epagis or Almarin or Coromega or Lovaza or Vascepa or icosapent ethyl OR ((fish n3 consum*) or (fish n3 intake) or (fish n3 diet*)) OR mediterranean n3 diet*

S7 growth OR ((child* n3 development) or gestational age or premature infant or low birth weight OR (gestat* and (age* or durat* or week*)) OR prematur* or preterm or pre-term OR (low n3 (birthweight or weight))

S8 newborn or neonat* OR Retinopathy n3 Prematurity OR retrolental fibroplasia* OR ADHD or attention deficit disorder* OR atopic n3 dermatitis

S9 autism OR autistic OR asperger* OR ados OR hypersensitiv* OR allerg* OR (Fetal AND growth AND retard*) OR (Embryo* AND Fetal Development) OR (Fetus OR ((fetal OR fetus OR intrauterine) AND (growth OR develop*)))

S10 Preeclamp* OR pre-eclamp* OR (Pregnan* AND Toxemi*) OR ((Gestation* OR pregnan*) AND (hypertens* OR toxemi*)) OR (gestat* AND (child* OR newborn* OR infan* OR neonat* OR baby OR babies OR pediatr* OR paediatr*)) OR (depression AND (postpartum OR postnatal OR post-partum OR post-natal OR post partum OR post natal OR ante-natal OR antenatal OR ante natal)) OR (grow* near/3 (child* OR infant* OR infancy))

S11 (congenital AND (vision near/3 disorder*)) OR ((learning near/3 disorder*) OR dyslexi* OR discalculi*) OR ((respiratory near/3 illness) OR asthma* OR wheez* OR respiratory syncitial virus)

S15 s7 OR s8 OR s9 OR s10 OR s11

S18 s1 OR s2 OR S3 OR S4

S19 s15 AND s18

==========

DATABASE SEARCHED & TIME PERIOD COVERED:
CAB ABSTRACTS – 1/1/2000-11/11/2014

LANGUAGE:
English

SEARCH STRATEGY:
ti("Child Development" OR (gestat* AND (age* OR durat* OR week*)) OR prematur* OR preterm OR pre-term OR ((Infant* OR baby) AND (birthweight OR birth-weight OR weight)) OR newborn OR neonatal OR (grow* AND (child* OR infant* OR infancy)) OR "Retinopathy of Prematurity" OR "retrolental fibroplasia" OR ADHD OR attention deficit disorder* OR "atopic dermatitis" OR (congenital AND ("vision disorder")) OR "learning disorder" OR "learning disorders" OR dyslexi* OR discalculi* OR "respiratory illness" OR asthma* OR wheez* OR respiratory syncitial virus OR autism OR autistic OR Asperger* OR ados OR hypersensitiv* OR allerg* OR (Fetal AND growth AND retard*) OR ((embryo* OR Fetus OR fetal OR fetus OR intrauterine) AND (growth OR develop*)) OR Preeclamp* OR pre-eclamp* OR ((Gestation* OR pregnan*) AND (hypertens* OR toxemi*)) OR (gestat* AND (child*or newborn* OR infan* OR neonat*or baby OR babies OR pediatr* OR paediatr*)) OR (depression AND (postpartum OR postnatal OR post-partum OR post-natal OR post partum OR post natal OR ante-natal OR antenatal OR ante natal)) OR (grow* AND (child* OR infant* OR infancy)))
AND
ti(omega-3 OR omega3 OR "omega 3" OR "essential fatty acid" OR "essential fatty acids" OR linolenic OR "fish oil" OR "fish oils" OR polyunsaturated OR pufa OR dha OR epa OR long chain OR longchain OR Docosapentanoic OR Docosapentaenoic OR Docosahexaenoic OR Eicosapentaenoic OR icosapentaenoic OR ((n 3 OR n3 OR n-3) AND (oil OR pufa OR fatty acid OR omega 3)) OR alpha linolenic OR alphalinolenic OR alpha-linolenic OR linolenate OR

cervonic OR timnodonic OR stearidonic OR butternut OR soybean OR pumpkin seed OR menhaden OR flax OR flaxseed OR flax seed OR linseed OR rape seed OR rapeseed OR canola OR soy OR soybean OR walnut OR mustard seed OR perilla OR shiso OR walnut OR "cod liver oil" OR "codliver oil" OR "marine oil" OR "marine oils" OR "marine fat" OR salmon OR mackerel OR herring OR tuna OR halibut OR seaweed OR anchov* OR sardine* OR Ropufa OR MaxEPA OR Omacor OR Efamed OR ResQ OR Epagis OR Almarin OR Coromega OR Lovaza OR Vascepa OR icosapent ethyl OR (fish AND (consum* OR intake OR diet*)) OR "mediterranean diet" OR (("Red blood cell" OR "red blood cells" OR phospholipid* OR plasma OR triacylglycerol OR cholesteryl OR ester OR adipos* OR fatty acid OR fatty acids OR erythrocyte OR ghost OR platelet* OR granulocyte OR neutrophil OR mononuclear OR LDL OR HDL) AND (EPA OR SDA OR stearidonic OR omega*))

Narrowed by:
Subject: hominidae; homo; man; human diseases; infants; food allergies; pregnancy; children; premature infants; allergies; women; neonates; infant formulae; asthma; randomized controlled trials; human milk; prematurity; fetus; mothers

Exclude:
Subject: rodents; muridae; animal models; mice; rats; pigs