Evidence Report/Technology Assessment Disposition of Comments Report

Research Review Title: *Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review*

Draft review available for public comment from August 19, 2015 to September 17, 2015.

Research Review Citation: Newberry SJ, Chung M, Booth M, Maglione MA, Tang AM, O'Hanlon CE, Wang DD, Okunogbe A, Huang C, Motala A, Timmer M, Dudley W, Shanman R, Coker TR, Shekelle P. Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review. Evidence Report/Technology Assessment No. 224. (Prepared by the RAND Southern California Evidence-based Practice Center under Contract No. 290-2012-00006-I.) AHRQ Publication No. 16(17)-E003-EF. Rockville, MD: Agency for Healthcare Research and Quality; October 2016. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Quality of Report	Superior	Thank you.
TEP Reviewer #2	Quality of Report	Superior	Thank you.
Peer Reviewer #1	Quality of Report	Good	Thank you.
Peer Reviewer #2	Quality of Report	Fair	Thank you. We hope we have addressed your comments adequately below.
TEP Reviewer #3	Quality of Report	Good	Thank you.
TEP Reviewer #4	Quality of Report	Superior	Thank you.
TEP Reviewer #5	Quality of Report	Superior	Thank you.
TEP Reviewer #1	General comments	The report is clinically meaningful. The target population and audience are (relatively briefly) defined in the introductory paragraph. Many other stakeholders could also be interested. The key questions are repeatedly reported and repeatedly answered, very clearly and explicitly. They are the most appropriate for the issue of omega-3.	Thank you. We don't think a further response is warranted
TEP Reviewer #2	General comments	This is an excellent review, comprehensive, clinically meaningful with well-defined outcome measures and target/study populations. The key questions are appropriate and explicitly stated. It requires a bit of further copy editing, particularly in the abstract V. line 48 and 52.	The report will undergo copyediting before posted as a final report.
Peer Reviewer #1	General comments	Considering most of the outcomes evaluated, it would be beneficial if the report had indicated whether differences were felt to be clinically meaningful in the instances when some level of strength of evidence yielded some effect. Most of the observations were for no effect.	To identify whether differences are clinically meaningful, we would need to know what are considered Minimum Clinically Important Differences (MCIDs) for these outcomes. We have not identified any published agreed-upon MCIDs) for the outcomes of interest to this report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General comments	The limitations of the studies reviewed appeared to be significant.	Yes, we agree and have attempted to delineate the limitations in the Discussion chapter, which we have augmented with additional limitations noted by some of the reviewers.
Peer Reviewer #1	General comments	Target populations were defined.	No response is warranted.
Peer Reviewer #1	General comments	Key questions were worded as to imply stronger emphasis on associations rather than causal relationships.	We did not intend to emphasize associations over causal relationships, although we did intend to include the results of prospective observational studies to compare their findings with those of RCTs. In fact, the key questions were taken directly from the original review, and purposefully not changed.
Peer Reviewer #1	General comments	The pagination and line counting used in this report makes it very difficult to assure comments rare accreting notated for the correct pages of text.	We apologize, but we have access to the line-numbered version of the report and make every effort to identify the text that corresponds to a comment.
Peer Reviewer #1	General comments	It appears that the majority of evidence demonstrated various strength of evidence for lack of effect or no effect (This reviewer is not sure why the different terminologies are used.).	It's true that most studies show inconclusive evidence. We have ensured that the wording for insignificant results or results of borderline significance is consistent throughout.
Peer Reviewer #1	General comments	It would be beneficial if the authors would provide comment when there is some level of evidence for a positive effect as to whether the difference is at a level of biological significance versus just statistical significance.	As noted, we have not identified any agreed-upon MCIDs for the outcomes of interest to this report.
Peer Reviewer #1	General comments	It is somewhat surprising the number of sites for which it is stated that the dates as well as study design were not reported. Since other details of the studies were abstracted, it is not clear whether this lack of detail is of any importance.	These omissions were a result of the way that the original tables were constructed: The information was inadvertently omitted when the tables were generated, and this oversight has been fixed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General comments	In the discussions related to biomarkers, it is not always clear as to what biomarker was assessed. In some cases different biomarkers were assessed in different studies evaluating the same outcome; however, no comment is made about the comparability of various biomarkers used. (The implications of this comment may also be implied in the Limitation section commented upon below.)	Data on the association between biomarkers and outcomes of interest were very limited, and each study assessed associations with different biomarkers. In almost no case did more than one study assess the association between a specific biomarker and an outcome of interest. Therefore, we were prevented in most cases, from being able to draw any conclusions. In the Results section, we now call attention to studies where outcomes were associated with a biomarker, in spite of a lack of apparent effect of an intervention on the outcome. We have noted this limitation in the Discussion chapter.
Peer Reviewer #1	General comments	The limitations expressed on pages ES-3 to ES-4 (also labeled pages 28 and 29 of 1219 and again included on pages 276-277 or pages 305 and 306 of 1219) and the statement related to the risk of bias raise a significant question of overall quality of the studies reviewed and consequently the interpretations made.	As part of the review process, we assess the study quality (risk of bias) of each study in duplicate with reconciliation of disagreements, using published assessment methods (Cochrane, Newcastle-Ottawa, McHarms). These risk-of-bias assessments are then used in assessing the overall strength of evidence for each conclusion.
Peer Reviewer #1	General comments	For reports of observational studies, there should be some discussion of the potential for other factors (besides omega-3 fatty acids) that may be different. Did authors of included studies assess whether there may have been associated factors that were also different between study groups?	We have added the lists of confounding factors considered in analyses in observational studies to our narrative descriptions of those studies, if we had not already included them, and they are also included in the evidence tables. Where authors have invoked confounding factors to explain their findings, we have noted that in the report text.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General comments	A point that is not clear to this reader is whether the studies used in the report made any adjustment of dietary intake of omega-3 fatty acids that were not specifically quantitated. Since all studies needed to have quantitation of omega-3 intake, how was the consumption of fish or other foods containing omega-3 fatty acids handled? Perhaps a brief description of the methodology to quantitate omega-3 levels for the included studies might be considered to be included in the methodology section. (Comments pertain to the maternal studies more than the child studies.)	As agreed upon with ODS and AHRQ as well as the Technical Expert Panel, we did not include studies that reported only intake of whole foods without quantification of the omega-3 fatty acid contents. We abstracted how intake was assessed (e.g., food frequency questionnaire) but not the reference for quantitation. We have noted this in the list of inclusion and exclusion criteria in the report.
Peer Reviewer #1	General comments	In the analyses, it was not clear if there was an attempt to assess an interaction between levels of omega-3 fatty acid intake and the total fat intake or the ratio of omega-3 to omega-6 intake. It is possible that outcomes may be influenced by relative intake levels and not just absolute intake levels. It may not be possible to conduct these types of analyses within the framework of the conducted review; however, perhaps some comment could be made to indicate this inability as another functional limitation within the report.	We recognize the potential importance of relative intakes. Unfortunately, we tried to abstract the information that would have enabled us to assess the relative intakes but these data were seldom provided across studies. We now address this issue as a limitation.
Peer Reviewer #2	General comments	What is the rationale for separating algal and fish oil sources of omega-3 FA supplementation in the primary analysis? Wouldn't it be prudent to group all the RCTs together, then perform a subgroup analysis based on source or composition and then present results separately based on source if the test for subgroups is significant. Is there any scientific rationale why DHA alone should be beneficial while DHA+EPA would not be? If so this should be included in report.	We have now completely redone the pooled analyses, pooling all n-3 FA interventions that address a particular outcome, followed up with the individual pooled analyses for specific n-3 FA. As for why DHA might be beneficial when DHA+EPA is not, we speculate that DHA might be the more active omega-3 and that studies that showed an effect of DHA alone may have used a higher dose of DHA than was given in studies of DHA+EPA or fish oil.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General comments	Treatment of the observational studies regarding maternal blood levels of omega-3 FA levels, I find suboptimal. Omega-3 blood levels are associated with education level, SES, certain ethnic backgrounds, smoking and overall maternal nutrition that may also be associated with pregnancy outcomes. Thus there is a likelihood of confounding by any (or all) of these factors on the association. Although ratings of observational study quality with Ottawa-Newcastle is standard, it is certainly non-sufficient in this case. Noting whether studies adjusted for these factors seems imperative regarding any evaluation of the evidence.	We have now included the evidence tables for observational studies, and these tables list the confounding factors (e.g., maternal smoking or alcohol use during pregnancy, parental smoking in the home postpartum, parental educational level) for each study. We also describe the factors for which authors controlled in the narrative descriptions where possible. Finally, we address this issue of confounding by both measured and unmeasured confounders in the Limitations section.
Peer Reviewer #2	General comments	Page 27 – mentioning the issue of confounding for observational studies in paragraph 3 seems imperative.	We have now added the issue of confounding for observational studies to the Limitations sections.
Peer Reviewer #2	General comments	Using the data from observational studies to increase the SoE for the association with birthweight, is not justified in my opinion because of the confounding issue.	We did not use the results of observational studies directly to increase the SoE of the birthweight studies (that is, we did not consider the risk-of-bias of individual observational studies in determining the limitations). But we did consider the consistency between RCT and observational data as one factor in assessing SoE (along with the consistency among RCTs themselves) when there were relevant observational studies that addressed the same outcomes.
Peer Reviewer #2	General comments	Individual discussion of the observational studies mentioning that they "controlled for potential confounders" is not sufficient since they may or may not have controlled for the same factors or the ones you deem important.	We have now listed the factors that each study controlled for in the narrative descriptions and the evidence table and we address the adequacy and relevance of these factors for the outcomes of interest in the Discussion/Limitations section.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General comments	Some analysis examining absolute DHA and EPA in supplementation and EPA:DHA and effects on association seem appropriate.	It's difficult to know how to take into account the absolute dose of DHA and EPA. For outcomes that had sufficient numbers of studies, we conducted random-effects meta-regression. We also rechecked the very small number of studies that did dose-response assessments and noted in the text that these studies did not see dose-response effects.
Peer Reviewer #2	General comments	Publication bias has been demonstrated to be a major issue in omega-3 studies. Funnel plots and egger's test should be conducted and presented for all outcomes.	We now present the results of Egger's and Begg's tests for outcomes that are significant.
TEP Reviewer #3	General comments	Yes, the report is clinically meaningful. It could be enhanced substantially if the authors consider adding 2 further outcomes in relation to the duration of gestation; early preterm birth <34 weeks and prolonged gestation >42 weeks. Both of these outcomes would often require major intervention and would give some sense of the importance and impact of the shift in gestation duration that was observed in the systematic review.	We did not identify any studies that assessed the risk for late term births (>42 weeks) and only 1 study appears to have reported the incidence of early preterm births (<34 weeks); we report this outcome.
TEP Reviewer #4	General comments	The report is clinically meaningful in that there are no strong effects that should change current clinical practice. The target population and audience are well defined. The key questions were readily identifiable and explicit.	Thank you. We don't think a further response is warranted.
TEP Reviewer #5	General comments	This is a very important summary because it provides an in-depth look at the research on omega fatty acids and both maternal and infant health outcomes. Calling out the specific categories, and then identifying the research outcomes is critical. I found it very usable and important to the daily practice of medicine	Thank you. We don't think a further response is warranted.
TEP Reviewer #1	Introduction	The introduction (pg 10 to 18 for me, excluding preface) is straightforward and clear, particularly pg. 10 to 13 (some Readers after these pages will skip directly to 303-309, that is, the conclusions).	Thank you. We don't think a further response is warranted.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Introduction	The introduction provides an excellent background for the review. My only suggestions are 1) the authors should more strongly emphasize that while the review is focused on N-3 FA's, the supplements provided study subjects in the included RCTs and Observational studies almost always include N-6 LCPUFAs as well as N-3 LCPUFAs and so in some ways these outcomes are a blended result of supplementation with both lines of LCPUFAs; 2) the post-natal infant outcomes are sometimes framed generally as "infants", rather than specifically describing the outcomes in premature infants vs. full-term infants. In all cases the maturity of the study infants should be explicitly stated since these are biologically and physically very different groups.	Studies of n-3 FA alone were included as were studies of n-3s plus n-6s. We mentioned in our list of study limitations that many interventions described as n-3 FA (especially DHA) actually included n-6 FA such as arachidonic acid (AA), particularly studies of infant formula supplementation, and that no studies assessed the effect of n-3FA/n-6 FA ratio. We have attempted to clarify for all postnatal outcomes whether the participants were preterm or term infants.
Peer Reviewer #1	Introduction	• Page v; Lines 42-46 (Also ES -10, line 48-57): To interpret data on birth weight, information about maternal weight gain should also be provided since increased levels of omega–3 intake could be associated with overall increase of calories and increased weight gain.	We agree that it would be helpful to have data on maternal weight gain and caloric intake to put data on birth weight into the proper perspective. Unfortunately, few studies took maternal weight gain into account in a multivariate analysis, and the studies that simply reported maternal weight gains by intervention group or exposure quantile reported it as group means, and these data can't be used in a meta-analysis, as they would need to be paired with their corresponding maternal intakes and infant birth weights..
Peer Reviewer #1	Introduction	• Page ES-1; lines 20-21: For clarity, it would be beneficial to mention that the omega-3 fatty acids found in these sources were derived from dietary intake of plants, nuts, or algae and other sources mentioned in the lines above.	We have added this information to the sentence in question: “ALA is found in plant foods, such as leafy green vegetables, nuts, and vegetable oils such as canola, soy, and flaxseed.”.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Introduction	• Pages ES-2 line 36 to ES-4 line 1: The questions used imply looking for associations and not causal relationships. I am not sure if this approach was intended.	We did not intend to emphasize associations over causal relationships, although we did intend to include the results of prospective observational studies to compare their findings with those of RCTs. In fact, the key questions were taken directly from the original review, and purposefully not changed.
Peer Reviewer #2	Introduction	Rationale for analyzing algal and murine omega-3 supplementation separately should go here.	We have now added pooled analyses that combine all sources of omega-3 FAs.
TEP Reviewer #3	Introduction	Satisfactory	No response seems to be needed.
TEP Reviewer #4	Introduction	The target population and audience are very well defined. The Key questions were readily identifiable and explicit. Figures in the Introduction were very helpful.	Thank you. We don't think a further response is warranted.
TEP Reviewer #5	Introduction	Good overview of the differences between the chemical compounds being addressed, and comparison to previous research overview	Thank you. We don't think a further response is warranted.
TEP Reviewer #1	Methods	The inclusion and exclusion criteria are justifiable and are justified. The search strategies are explicitly stated and are also logical. Outcome measures and statistical methods appropriate. Statistics as discussed and considered/used, superb, as far as I understand.	Thank you. We don't think a further response is warranted.
TEP Reviewer #2	Methods	Inclusion and exclusion criteria are fully justifiable and very well thought through. The search strategies similarly are explicitly stated and logical with clear definitions and criteria for outcome measures. The statistics are completely appropriate.	Thank you. We don't think a further response is warranted.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Methods	The search strategies appear reasonable. However, in the studies reviewed, it is difficult to truly assess what change in omega-3 status was actually achieved. The intervention usually only had level of supplements delivered, in some cases an estimate of dietary intake, rare reporting of baseline intake of omega-3 and relative levels of all fatty acid classes, and no information whether the omega-3 fatty acids were being metabolized or impacting plasma, cellular, or tissue levels (different biomarkers used in different studies with no info available on comparability of biomarkers.	Yes, the reviewer is accurate in the omissions he identifies in the literature. We have addressed these kinds of limitations in the Discussion section under "Limitations," where we describe the limitations of the studies that result in the lack of ability to assess participants' initial or final omega-3 status and the possible role of this factor in outcomes of supplementation.
Peer Reviewer #2	Methods	methods for finding papers seems appropriate. I would make the following suggestions as in general comments above. (1) presenting a test for subgroup differences for DHA-only vs DHA+EPA.	We have now added overall pooled analyses to the existing analyses, and show the meta-analyses by type of n-3 FA on the same forest plot. We think these forest plots show the differences in pooled effect sizes and that meta-regression on the type of n-3 FA is not needed in addition.
Peer Reviewer #2	Methods	(2) meta-regression or subgroup analysis based on omega-3 dosing.	We have run meta-regressions for dose for studies of maternal intakes; however, for studies of infant intake (formula supplementation), we believe that meta-regression would not be appropriate because supplementation levels are expressed in several different ways across studies, and because no studies ever report actual intakes.
Peer Reviewer #2	Methods	(3) methodology regarding whether important confounders in observational studies	We have described the factors for which observational study findings were corrected. We have also now addressed some of the factors that observational studies and long-term follow-ups of RCTs have often failed to consider, e.g., postnatal parental smoking, indices of socioeconomic status, and parental and child education.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Methods	(4) assessment of publication bias	We have now provided Egger's and Begg's statistics in the text for pooled analyses that showed significant effect sizes.
TEP Reviewer #3	Methods	Satisfactory	We don't think a response is needed.
TEP Reviewer #4	Methods	Search strategies were excellent and clearly stated. The inclusion and exclusion criteria are appropriate and justifiably comprehensive. It was helpful to have the Key Question associated with each criterion area.	Thank you. We don't think a further response is warranted.
TEP Reviewer #4	Methods	Pediatric Outcome measures--cognitive development: The ones listed are not representative of what actually used in the various studies summarized. I would revise to the following because they are mentioned in the summary of studies and psychologists will recognize these standard developmental batteries. *Bayley Scales of Infant Development (BSID, BSID-II, BSID-III) *Fagan Test of Infant Intelligence *Neonatal Behavior Assessment *Griffith mental Development Scale *Kauffman Assessment Battery for children (K-ABC) *MacArthur Communicative Development Inventory *Wechsler Primary and Preschool Scale of Intelligence-R *Mullen Scales of Early Learning *McCarthy Scales of Children's Abilities (MSCA) *Communicative Development Inventory (CDI) *Ages and Stages Questionnaire (ASQ) *Wechsler Intelligence Scale for Children (WISC)	We have revised the PICOTs (description of inclusion and exclusion criteria) to reflect the outcome measures that were actually reported in studies we identified, as the reviewer suggests.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Methods	In general statistical methods appear appropriate. I am wondering the following, however: When studies were combined to look at infant/child cognitive outcomes, and if the studies used different versions of the BSID (e.g. BSIDII vs. BSID-III) were outcome results modified to reflect the degree of relationship between the two versions of the battery? (e.g., BSID-I scores generally higher than by BSID-II scores when administered to the same child).	We didn't pool any studies with cognitive outcomes in the draft we submitted for review, partly for the reason the reviewer states. If we were to pool studies, we would only do so if the outcome measures were the same or if we calculated a standardized mean difference. We have subsequently reassessed the studies identified for the current report and the studies included in the original report. We did not pool studies that used different versions of the test.
TEP Reviewer #4	Methods	I think there should be some mention of the extreme heterogeneity of the cognitive/developmental batteries and tests among the various studies looking at cognitive outcomes. These are not inter-changeable and really get at different aspects of cognitive development.	We have now added a discussion of this point in the Limitations section of the Discussion.
TEP Reviewer #5	Methods	I very much appreciated the specific categories being addressed, with consideration for maternal neonatal and infant outcomes. The research was clearly compared based on the type of fatty acid exposure	Thank you. We don't think a further response is warranted.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Results	An advantage of the present systematic review is the pre-existence of the previous 2004 draft, so Authors can go over, briefly summarizing what was then recolonized and what is new now. In my opinion details and characteristics are more than sufficient, and very clearly described, once more. The methodology used is the best guarantee of the maximum possible objective approach. As a personal observation , for the research in fatty acids it is often difficult to interpret a "no result" as neutral or negative. There are problems, in Tables, difficult to avoid, for instance, the Notenboom study (Notenboom ML, Mommers M, Jansen EH, et al.Maternal fatty acid status in pregnancy and childhood atopic manifestations: KOALA Birth Cohort Study. Clinical & Experimental Allergy. 2011,41:407-16) keeps for structural and methodological reasons more than 200 pages (666 to 876) in Tables, that is 18% of the draft. I admit not to be able to supply a useful suggestion, in order not to get the reader lost. Maybe this is a feature present in general within the Tables reporting allergy-related studies.	To make the tables easier to read, we have substantively revised them, removing all duplicate results and leaving only the results that pertain to the outcomes addressed in that section of the report.
TEP Reviewer #2	Results	There is ample detail in the results section and the included studies are well described. Please see my general comments for my only suggestions re key messages. Figures and tables as well appendices are well-done. The list of studies is comprehensive and doesn't include studies that should have been excluded. I don't believe that 2 very recently published studies were included and should be considered: Almaas et al. Pediatrics 2015.135:6:972-80 and Collins CT et al. BMJ Open. 2015. DOI 10.1136	The study by Collins and colleagues was identified in the searches we conducted while the report was in review, so we now include it. The Almaas article is a 7-year followup to the study first reported by Westerberg and Henriksen: we have added it to the description of the findings of this study.
Peer Reviewer #1	Results	See also above comment (in Methods) and comments on attached document (general comments included above).	We believe we have addressed the comments above and in the document.
Peer Reviewer #2	Results	If the current methodology remains this presentation seems fine. But i would view publication bias analysis as essential here.	We have added Egger's and Begg's statistics for significant findings.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	Satisfactory. Some minor comments: Neurodevelopment section- missing pregnancy RCT with motor outcomes at 4 & 5.5 years Escolano-Margarit MV, Ramos R, Beyer J, Csabi G, Parrilla-Roure M, Cruz F, et al. Prenatal DHA status and neurological outcome in children at age 5.5 years are positively associated. Journal of Nutrition 2011;141(6):1216-23.	We had inadvertently excluded this article as one of our reviewers thought it was a small observational study (our exclusion criteria included sample size being less than 250); however we rereviewed and realized it was a posthoc analysis to an RCT so we have included it in the final report
TEP Reviewer #3	Results	Pg 122 line 37 “inc0onsistent”	We have fixed the typo. Thank you!
TEP Reviewer #3	Results	Pg 123 line 23 Table X	We have inserted the correct table number. Thank you!
TEP Reviewer #3	Results	Pg 130 lines 27-29 {#4266} etc	When we inserted EndNote references, we inadvertently missed a number of references in the tables. These have since been corrected.
TEP Reviewer #3	Results	Pg 132 line 20. Author name “van Goor”-this study is presented in the tables twice, pg 132 & pg 133-134 Pg 170 line 8-looks like Gustafson (ref 79) results should be under Neurodevelopment outcome if motor	In the version of the report that was sent for review, we repeated all study outcomes in each of the tables in which a study appeared. We have revised the tables so that only the relevant outcomes for that section of the report are included in each table. The Van Goor study, which reports on abnormal movements, is included in the Neurodevelopment section. The Gustafson study was described narratively in the section on cognitive outcomes, although one domain of the Neonatal Behavior Assessment did measure motor development.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	Cognitive Development section: page 169-Missing 2x n-3 RCT's with Bayleys, etc Mulder KA, King DJ, Innis SM. Omega-3 fatty acid deficiency in infants before birth identified using a randomized trial of maternal DHA supplementation in pregnancy. Plos One 2014;9(1):e83764. Ramakrishnan U, Stinger A, DiGirolamo AM, et al. Prenatal Docosahexaenoic Acid Supplementation and Offspring Development at 18 Months: Randomized Controlled Trial. PLoS One 2015; 10(8): e0120065.	We had inadvertently excluded this article; we have since included it.
TEP Reviewer #3	Results	Pg 170 line 18-22 & 178 Makrides DOMInO trial also 4 year cognitive, language, executive function and behaviour outcome (note the 2010 paper also reports language outcome from the Bayley III) Makrides M, Gould JF, Gawlik NR, et al. Four-year follow-up of children born to women in a randomized trial of prenatal DHA supplementation. JAMA 2014; 311(17): 1802-4.	We have now included the piece in our Results; we had inadvertently excluded it as it was a letter to a journal..
TEP Reviewer #3	Results	Pg 170 line 23-28 & 183 Dunstan trial also 12 year cognitive outcome & original paper cited also has language & behaviour outcome at 2.5 years Meldrum S, Dunstan JA, Foster JK, Simmer K, Prescott SL. Maternal fish oil supplementation in pregnancy: a 12 year follow-up of a randomised controlled trial. Nutrients 2015;7(3):2061-7. (listed in table separately on page 185-should be part of Dunstan study on pg 183) Pg 170 line 44-49 & table pg 192Helland trial also 4 year cognitive outcome Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. Pediatrics 2003;111:e39-44.	We thank the reviewer for pointing out these omissions. Meldrum (2015) has now been linked to the Dunstan trial. The birth outcomes from Helland, 2003 were included in the original report. We now report the cognitive outcomes in the section on cognitive development.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #3	Results	Pg 171 line 18-26 & 177 Makrides DINO trial also 7 year cognitive, behaviour, visual and attention outcomes Collins CT, Gibson RA, Anderson PJ, McPhee AJ, Sullivan TR, Gould JF et al. Neurodevelopmental outcomes at 7 years' corrected age in preterm infants who were fed high-dose docosahexaenoic acid to term equivalent: a follow-up of a randomised controlled trial British Medical Journal-Open. 2015;5(3). doi:doi:10.1136/bmjopen-2014-007314	We have now included the Collins article in our revised Results section on visual function development
TEP Reviewer #3	Results	Pg 171 line 44, 172 line 44-title is visual acuity instead of cognitive development?	Thank you. We have corrected the title.
TEP Reviewer #3	Results	Pg 201 & pg 203 includes a report of Autism spectrum disorder and ADHD symptoms after DHA supplementation (preterm infants) Collins CT, Gibson RA, Anderson PJ, McPhee AJ, Sullivan TR, Gould JF et al. Neurodevelopmental outcomes at 7 years' corrected age in preterm infants who were fed high-dose docosahexaenoic acid to term equivalent: a follow-up of a randomised controlled trial British Medical Journal-Open. 2015;5(3). doi:doi:10.1136/bmjopen-2014-007314	We have now included the Collins article in our revised Results section on risk for ASD and ADHD.
TEP Reviewer #4	Results	In general results present enough detail and studies are clearly described. I would have preferred that the actual cognitive or developmental test administered to an infant or child be listed in the table listing studies for Cognitive Development (Table 17).	In the column labeled "Results," we provided the name of the test (outcome measure) as reported in the publications. However, we have reviewed the included studies to make sure we provided the correct names.
TEP Reviewer #5	Results	YES; the summary clearly calls out specific findings where the Fatty acid findings are significant, and where not	Thank you. We don't think a further response is warranted.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Discussion/Conclusion	Pages 303 to 309 are central for the Readers, and maybe most people, even if highly interested, will concentrate only on these pages. In general findings and results are very well summarized, and I find the next section on "limitations" particularly helpful for the interpretations of the results . As a matter of fact, the "mastodontic" amount of research on fatty acids has delivered a small mouse, due to the heterogeneity in study designs. Maybe I would emphasize clearer that, along with the fatty acid assessment at time 0 and time 1 of RCTs , participating subjects should undergo a parallel study on recognition of FADs polymorphisms to reach more definitive conclusions (and definitely saving more money at long term).	We have added a brief discussion of the need for studies to assess FADs polymorphisms to the section on Future Research recommendations.
TEP Reviewer #2	Discussion/Conclusion	The major findings of this review are quite clearly stated as are the limitations. See my comments above about the Almaas et al and Collins et al studies from this year that I don't believe were included and should be considered. The future research section is clear and provides good direction for future studies.	Thank you. We have added the studies as suggested.
Peer Reviewer #1	Discussion/Conclusion	The strongest implication is that further research is needed in better designed studies.	No response seems to be needed.
Peer Reviewer #2	Discussion/Conclusion	seem fir the most part appropriate given the initial findings with the caveat that there are several methodological issues with publication bias and confounding in regard to observational studies that may really affect conclusions.	We have now calculated publication bias for all pooled analyses that showed significant effect sizes. Publication bias was not observed for any of these outcomes. We address the concerns regarding unmeasured confounders in the section of the Discussion on limitations.
TEP Reviewer #3	Discussion/Conclusion	Yes	No response seems to be needed.
TEP Reviewer #4	Discussion/Conclusion	Limitations are well described and implications of the major findings are appropriately cautionary. The future research section is clear and could be easily translated except for real world budget limitations that probably preclude large enough studies to obtain definitive results.	Thank you. No further response seems needed.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Discussion/Conclusion	In several places, the authors use terms such as "non-significant decrease in..." some measure. Strictly speaking, one doesn't find a non-significant decrease or increase; one finds significance or not. It could be that the authors were using the term "non-significant" to mean "minor" or "not significant clinically". If so, this latter wording should be used to be clear.	The reviewer raises a good point. We used such wording mainly when study authors reported a difference but even their own statistics did not bear it out. We've gone through the report and removed the term “non-significant.” In a very small number of cases, when confidence intervals suggested the possibility of borderline significance, we stated that the differences were insignificant but that the confidence intervals suggested possible borderline significance. . Regarding clinical significance, unfortunately, we have no benchmark for clinically meaningful differences for any of the outcomes.
TEP Reviewer #5	Discussion/Conclusion	YES; the summary shows how important it is to understand which category of fatty acid was being studied, and how limiting the data are when research categories are "lumed"	No response appears warranted.
TEP Reviewer #1	Clarity and Usability	This new report is a further proof on how it may be difficult to get precise answers to questions linking nutrients and health outcomes (a most recent example is provided by probiotics) in spite of hundreds of studies. Besides heterogeneity of study designs, also progresses of investigations through the years may partially account for some gaps between research and expected results (for instance, the progress in genetic studies). The report is by no doubt well-structured and organized, and THE MAIN POINTS CLEARLY SUMMARIZED . The conclusions are very relevant, for me, 1 to better understand the limits of studies on n-3 LCPUFA so far, 2 to indicate the need of major homogeneity in studies (FA status, haplotypes, as already mentioned) and, 3, maybe also focus on some subgroup of populations more prone to disease. I may also accept that , at this point (of the evidence), the indications for supplementations with LCPUFA are indeed limited.	Thank you! No additional comment appears warranted.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Clarity and Usability	I found this report to be well structured and well organized and in fact to be a "good read". The conclusions are highly relevant to policy and practice and largely confirm the findings of the previous review on this topic.	Thank you. No response appears warranted.
Peer Reviewer #1	Clarity and Usability	See comment regarding the limitations of the studies reviewed.	We are not sure which comment the reviewer is referring to.
Peer Reviewer #2	Clarity and Usability	adding non-significant results to summary, clearly separating observation from RCT results would be helpful.	To keep the abstract and summary at a manageable length, we, did not list the non-significant results or the conclusions with insufficient strength of evidence in the abstract or summary. We have added a table (Appendix G) that lists outcomes by study, which should help highlight differences between observational studies and RCTs.
TEP Reviewer #3	Clarity and Usability	Yes	Thank you. We don't think an additional response is needed.
TEP Reviewer #4	Clarity and Usability	Nicely written, clear and well organized. The lack of clear effects, and heterogeneity of the study methods makes policy or practice decisions moot at this time and I think the authors made that point. The report does offer new information and does suggest appropriately, where future research might be most beneficial.	Thank you. We don't think an additional response is needed.
TEP Reviewer #5	Clarity and Usability	I particularly like how direct the categories were at the very start and how the research is looking at important factors that have all been considered associated with improved health outcomes with supplementation. This is a clinically useful report AND it highlights the important future research, particularly around dose supplementation	Thank you. We don't think an additional response is needed.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 Mardi Mountford, V.P. Infant Nutrition Council of America	General	The Infant Nutrition Council of America (INCA) is responding to the draft Agency for Healthcare Research Quality (AHRQ) report of findings from the systematic review on the effects of omega-3 fatty acids (n-3 FA) on maternal and child health outcomes. INCA is an association of manufacturers and marketers of formulated nutrition products, e.g., infant formulas and adult nutritionals. The draft report provides an important update of the scientific knowledge from 117 recent studies evaluating the effects of n-3 FA on health outcomes.	Thank you. We don't think an additional response is needed.
Public Reviewer #1 Mardi Mountford, V.P. Infant Nutrition Council of America	General	As noted in the report, standardization of n-3 and n-6, selection of clinically important outcomes, and baseline n-3 fatty acid intake are factors that need to be considered in future randomized controlled clinical trials. The report notes limitations due to variations in the n-3 fatty acids, methodologies including study and intervention duration, and outcome assessment in published studies to date. Additional confounders include the multifactorial nature of outcomes such as cognition and visual development that may add to mixed or inconsistent results. Thus, caution in making scientific conclusions from meta-analyses when data is from studies with divergent methodologies, is warranted.	Thank you. No further response is needed.
Public Reviewer #1 Mardi Mountford, V.P. Infant Nutrition Council of America	General	INCA members take very seriously their responsibility to provide safe and nutritious infant formulas to the millions of infants fed infant formula, often as the sole source of nutrition. The addition of docosahexaenoic acid (DHA) and arachidonic acid (ARA) to infant formula is modeled on the levels present in breast milk. U.S. infant formula manufacturers currently offer formulas containing DHA and ARA which have been safely fed to millions of infants for years. With the addition of these n-3 FAs to infant formulas, the industry continues its commitment to provide the best nutrition for infants whose mothers cannot or choose not to breastfeed.	No response needed

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 Mardi Mountford, V.P. Infant Nutrition Council of America	General	Formulas containing DHA and ARA have been shown to provide visual and mental development similar to that of the breastfed infant. The decision to supplement formulas with these nutritional long-chain polyunsaturated fatty acids (LCPUFAs) was made following years of research studying the clinical effects of both DHA and ARA in infants. The use of LCPUFAs in infant formulas has been reviewed and supported by the U.S. Food and Drug Administration, the American Dietetic Association and the Dietitians of Canada, the Codex Alimentarius Commission, the European Society for Paediatric Gastroenterology and Nutrition, the World Association of Perinatal Medicine and Child Health Foundation, the Food and Agriculture Organization and World Health Organization, the Commission of European Communities and the National Academy of Sciences.	We acknowledge that not all trials included a breast fed group for benchmarking and that we did not include the data when they did, as the breastfed group is not randomly generated whereas the intervention and control groups are randomly generated.
Public Reviewer #1 Mardi Mountford, V.P. Infant Nutrition Council of America	General	DHA and ARA are considered to be “building blocks” for the development of brain and eye tissue. Research has demonstrated that DHA and ARA, both present in human milk, are physiologically important in prenatal and postnatal life during the period of rapid brain and eye development and throughout life as well. DHA and ARA have been shown to rapidly accumulate in the brain during the last trimester prenatally and the first two years postnatally, and pre-clinical studies have also demonstrated their importance in visual and neural systems.	Again, we acknowledge that not all trials included a breast fed group for benchmarking and that we did not include the data when they did, as the breastfed group is not randomly generated whereas the intervention and control groups are randomly generated.
Public Reviewer #1 Mardi Mountford, V.P. Infant Nutrition Council of America	General	U.S. infant formula manufacturers continue to evaluate the potential benefits of adding nutritional fatty acids to infant formulas and look forward to additional systemic reviews with data from studies with more standardized methodologies. Thank you for your consideration. Please let me know if you have any questions.	Thank you for reviewing the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	General	The Global Organization for EPA and DHA Omega-3s (GOED) is an association of processors, refiners, manufacturers, distributors, marketers, retailers and supporters of products containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids. GOED's membership represents a broad range of businesses, from small entrepreneurs to multinational food companies. The Organization's objectives are to educate consumers about the health benefits of EPA/DHA and to collaborate with government groups, the healthcare community and the industry on issues related to omega-3s, while setting high standards for our business sector. As such, our members have a profound interest in ensuring that valuable information regarding EPA and DHA is communicated to consumers in a meaningful and timely way. Thus said, we appreciate the opportunity to provide comments on the draft report "Omega-3 Fatty Acids and Maternal and Child Health: An Updated Systematic Review."	Thank you for taking time to review the report.
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	General	The Agency for Healthcare Research and Quality (AHRQ) is to be commended for its efforts in compiling and analyzing vast amounts of data; however, given the importance and implications of this report, it should be noted that there are a number of shortcomings that ultimately undermine confidence in the reliability of the conclusions. From our perspective, the totality of scientific evidence was not considered and as a result this may have contributed to an unintended bias. This is due, in part, to the methodological approach which suffered from unnecessary restrictions along with arbitrary and inconsistent approaches to data analysis.	This systematic review was conducted according to the AHRQ Methods manual, realizing that we were charged to update an existing report. We have made every effort to be transparent in our description of our methods and decisions. Decisions regarding criteria for study inclusion and analysis were made by the research team based on the original report and for new outcomes, in consultation with a technical expert panel

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 **Harry B. Rice, PhD** **VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35**	General	With regard to AHRQ's own Effective Health Care (EHC) Program principles, the current draft report falls short. The EHC program follows three key principles that guide the conduct of systematic reviews including: 1) relevant and timely; 2) objective and scientifically rigorous; and 3) transparent - allowing for public participation to increase confidence in the integrity and credibility of reviews commissioned under the EHC program.[1] In particular, the current draft falls short with regard to critical aspects of scientific rigor, as detailed in the methodological issues outlined below, and transparency as the report suffers from a lack of clarity that erodes confidence in the reliability of the conclusions reached. The issues outlined below are sufficient to warrant a second opportunity for public review of the draft report after the issues outlined have been addressed. [1]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. Available online at http://www.effectivehealthcare.ahrq.gov/ehc/products/60/318/CER-Methods-Guide-140109.pdf	As described, the review followed the most recent Methods Guide and every effort was made to describe as transparently as possible the methods as well as any decisions that deviated from decisions that drove the original report. A technical expert panel also guided the decisions regarding outcome measures, interventions to include, and all inclusion and exclusion criteria. The search strategies were based on the original report with modifications to accommodate new outcomes of interest. All titles and abstracts identified by searches were dually screened for inclusion with reconciliation of disagreements. All data were dually abstracted or singly abstracted with review by a second reviewer, and all risk of bias and strength of evidence determinations were made by dual assessment. Decisions regarding exclusion and inclusion appear in the appendices and all data will be publicly posted.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Methodological Issues - Study Identification	• Searches were conducted from 1/1/2000-10/8/2014 (Appendix A. Search Strategy). For newly added topics, AHRQ referenced “mined articles” to identify any studies prior to 1/1/2000 and cross checked studies from the original report (page 8). An electronic search would have permitted a more reliable assessment of the evidence. MESH terms were introduced for docosahexaenoic acid in 1988 and fish oil in 1983. Mined articles may not reflect earlier, pivotal studies. The bottom line is that this strategy for evidence discovery may have limited access to older publications.	This review was largely an update of a prior review. Customarily, update searches commence with the publication year one year prior to the latest search date of the original review. For this review, we actually went back to the year 2000, 4 years prior to the original searches. For the newly added topics, with the agreement of the expert panel, we did rely on reference mining to identify studies with publication dates older than 2000. Two factors virtually ensure that we did not miss a single pivotal study: 1) the numbers of studies we identified on the newer outcomes that preceded 2000 through reference mining (and we reference mined every single included study) and 2) the fact that none of the reviewers identified any older studies we missed on the newer outcomes, even though these were their areas of expertise and they did identify several newer studies we had missed.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Methodological Issues - Study Identification	• Electronic search strategy was limited to English language publications. While only one study is listed as being excluded due to non-English language, the electronic search strategy was limited to English language publications. Thus, fewer were found and the number of pertinent foreign language publications was likely much greater than that reflected by the one excluded study. The AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (ECER Guide) notes on page 142 that restricting to English language publications should be avoided as it increases the risk of selection bias. The ECER Guide goes on to note that of EHC reviews conducted prior to 2014, 71% likely suffered from selection bias due, at least in part, to English language restrictions.	The original report did not limit its searches to English-language articles; nevertheless, that research team identified only one non-English language study that met inclusion criteria. Given this finding and the increase in the scope of work for this review, technical expert panel supported the decision to limit inclusion to English language studies, with the proviso that if reference mining or peer reviewers identified non-English language studies that otherwise met inclusion criteria and could be translated, we would include them. No non-English studies were identified. Finally, the report will be used in the US the likelihood that a non-English language study would have enrolled a population with strong applicability to the population of interest is extremely small.
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Methodological Issues - Study Identification	• Search strategy was inadequate to identify all pertinent studies. Despite a well-designed search strategy, it would appear that the strategy was insufficient to identify the complete evidence base. What follows is a list of pertinent studies not identified by AHRQ for the current draft report. Studies relevant to various outcomes including: gestation length, neurological development and cognitive development are identified, but the list is not meant to be exhaustive.	We are confident our search strategy was adequate, because all but one of the studies the commenter listed as not having been identified in our searches were in fact identified and "excluded" from our count of new studies because they were previously identified for the original report. We now provide an appendix that lists those studies, to help readers. We also provide responses regarding our decisions to exclude particular articles below.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Methodological Issues - Study Identification	**Gestation length** Smuts CM, Huang M, Mundy D, Plasse T, Major S, Carlson SE. A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. Obstet Gynecol. 2003 Mar; 101(3):469-79. **Note:** Gestation increased by 6.0 +/- 2.3 days (P =.009) in the higher DHA group. **Note:** Two different Smuts et al., 2003 publications were cited in "Figure 6. Incidence of premature birth – DHA vs. placebo" found in the section entitled "Length of Gestation (or Gestational Age) and Preterm Birth", but the full citations were not provided in the "References".	Yes, the two data points are from two different 2003 studies by Smuts et al., cited in the original report. We now include these two references in the appendix that lists studies included from the original report.
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Methodological Issues - Study Identification	**Neurological development** Cheatham CL, Nerhammer AS, Asserhoj M, Michaelsen KF, Lauritzen L. Fish oil supplementation during lactation: effects on cognition and behavior at 7 years of age. Lipids 2011; 46:637–645. **Note:** Breast-feeding Danish women were evaluated for the impact of supplementation during the first 4 months of lactation on cognitive test scores at 7 years of age. This study found a faster speed of information processing in children of previously supplemented mothers, and lower scores for inhibitory control/working memory in children with a higher DHA status at 4 months.	Thank you for identifying this study. The MeSH terms used to catalog this article did not allow it to be captured in the PubMed search we conducted (which followed the search strategy employed for the original report for this group of outcomes). We have now included it in the report. We followed the exact search strategy used for the original report. We cannot explain why this one study should have been missed, but the expert panel did not identify other studies that were missed by the searches.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 **Harry B. Rice, PhD** **VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35**	Methodological Issues - Study Identification	**Neurological development** Gale CR, Marriott LD, Martyn CN, Limond J, Inskip HM, Godfrey KM, Law CM, Cooper C, West C, Robinson SM. Breastfeeding, the use of docosahexaenoic acid-fortified formulas in infancy and neuropsychological function in childhood. Arch Dis Child 2010; 95:174–179. Note: This study was excluded due to < 250 subjects, but based on "Methods Guide for Effectiveness and Comparative Effectiveness Reviews", the study should not have been excluded.	We stated in our SR protocol and methods section that because of the vast scope of the review and outcomes of interest, and because we had to include both randomized controlled trials and observational studies, including observational studies not considered for the original report, we had to impose some limits to the studies we could include. With the guidance of the expert panel, we decided to limit inclusion of observational studies to those of 250 or more participants unless we found no other studies for a particular outcome. Including larger studies also helped ensure that we reviewed results with the greatest methodological rigor.. Importantly, for the primary outcomes reported in this study, the availability of several randomized controlled trials provided evidence on this topic.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 **Harry B. Rice, PhD** **VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35**	Methodological Issues - Study Identification	**Neurological development** Morales E, Bustamante M, Gonzalez JR, Guxens M, Torrent M, Mendez M, Garcia-Esteban R, Julvez J, Forns J, Vrijheid M, Molto-Puigmarti C, Lopez-Sabater C, Estivill X, Sunyer J. Genetic variants of the FADS gene cluster and ELOVL gene family, colostrums LC-PUFA levels, breastfeeding, and child cognition. PLoS One. 2011; 6:e17181. **Note:** Spanish children previously bottle-fed formula without added LC-PUFAs had an 8-to 9-point disadvantage in cognitive scores assessed at 14 months or at 4 years if they were homozygous for FADS genotypes linked to a low endogenous LC-PUFA synthesis compared to a genotype leading to more active LCPUFA formation. Koletzko et al., 20144 noted that "Assuming that FADS genotypes are distributed at random in the population and are not related to the decision to breast-feed (the concept of 'mendelian randomization'), these data support a causal relationship between LC-PUFA supply during lactation and status in infancy and later cognitive achievements.	The outcomes of the study by Morales were considered beyond the scope of the study because we were asked to assess the benefits of omega-3 FA supplementation or exposure for the general public. However, we have added a brief comment on the growing evidence for epigenetic influences on effects of supplemental n-3 FA in the Discussion.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 **Harry B. Rice, PhD** **VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35**	Methodological Issues - Study Identification	**Neurological development** Steer CD, Davey Smith G, Emmett PM, Hibbeln JR, Golding J. FADS2 polymorphisms modify the effect of breastfeeding on child IQ. PLoS One 2010; 5:e11570. **Note:** This article reported on the exploration of the interaction of postnatal breast-feeding and variation in the genotypes for FADS enzymes with regard to IQ scores assessed at about 8 years of age in 5,934 children born in the early 1990s in the UK. Breast-feeding was associated with higher IQ scores than bottle-feeding, which was not LC-PUFA supplemented or enriched at the time of the study. In children with a FADS genotype linked to a low endogenous LC-PUFA synthesis, breast-feeding supplying LC-PUFA provided an added benefit of more than 4 IQ points at school age compared to infants with a genotype supporting a more active LC-PUFA formation.	This study did not directly consider omega-3 fatty acids, but rather assessed the benefits of breastfeeding. Moreover, the outcomes of the study were considered beyond the scope of our review, as the study considered the effects of a genetic polymorphism, whereas this review is intended to assess the benefits of omega-3 FA supplementation or status for a general population. However, we have added a brief discussion on the growing evidence for epigenetic influences on effects of supplemental n-3 FA in the Discussion.
Public Reviewer #2 **Harry B. Rice, PhD** **VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35**	Methodological Issues - Study Identification	**Cognitive Development** Although meta-analyses in this area are fraught with heterogeneity, in dose interventions, selected outcomes and method of outcome assessment, it should have been noted that these studies do not adjust for genetic variations in FADS genotypes. Moreover, evidence for the benefit of a post-natal supply of LCPUFA's can be derived from gene interaction studies that report greater benefits of breastfeeding, which provide preformed LCPUFAs, in infants genetically determined to have lower LCPUFA synthesis (Koletzko et al., 20144, Steer et al., 2010, Morales et al., 2011). A systematic review by Koletzko et al, 20144 identified a trend toward a greater likelihood of benefit with formula doses of > 0.32% DHA and 0.64% ARA and a longer duration of higher post-natal supplementation up to 1 year of age. The following studies should have been considered:	We did not include prior systematic reviews in this review but did check references cited to ensure that we included any relevant citations (we had included one prior systematic review in the draft that was submitted for review, but we subsequently decided to review and abstract data from the original studies instead). We did not include studies that merely compared breastfed with formula fed infants because breastfed infants are not a randomly selected group and results of such studies have too many confounding factors.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Methodological Issues - Study Identification	[continued from above] Willetts P, Forsyth S, Agostoni C, Casaer P, Riva E, Boehm G. Effects of long-chain PUFA supplementation in infant formula on cognitive function in later childhood. Am J Clin Nutr 2013; 98: 536S–542S. **Note:** IQ scores of children who were fed a formula containing either LC-PUFAs or no LCPUFAs did not differ at age 6 y. However, children who received LC-PUFAs were faster at processing information compared with children who received unsupplemented formula. Variation in the dietary supply of LC-PUFAs in the first months of life may have long-term consequences for the development of some cognitive functions in later childhood.	Again, thank you for identifying this study.
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Methodological Issues - Study Identification	[continued from above] Colombo J, Carlson SE, Cheatham CL, Shaddy DJ, Kerling EH, Thodosoff JM, Gustafson KM, Brez C. Long-term effects of LCPUFA supplementation on childhood cognitive outcomes. Am J Clin Nutr 2013; 98: 403–412. **Note:** LCPUFA supplementation did not influence performance on standardized tests of language and performance at 18 months; however, significant positive effects were observed from 3 to 5 years on rule-learning and inhibition tasks, the Peabody Picture Vocabulary Test at 5 years, and the Wechsler Primary Preschool Scales of Intelligence at 6 years. Effects of LCPUFAs were not found on tasks of spatial memory, simple inhibition, or advanced problem solving.	Again, thank you for identifying this study.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Study Selection criteria	• A list of inclusion and exclusion criteria is requested. A PICOT format is used to identify the eligibility criteria via a series of questions. While PICOT is useful for topic development and refinement, failure to summarize the resulting inclusion and exclusion criteria in a clear and concise fashion (e.g. summary table as outlined in the AHRQ ECER Guide) would increase the clarity of the report and thus transparency. The current approach creates confusion, potential for misunderstanding and results in a general lack of transparency. No clear strategy is provided that identifies how a study is to be evaluated for exclusion. As stated in the 2009 PRISMA guidance for reporting systematic reviews and meta-analyses of studies, "Authors should unambiguously specify eligibility criteria used in the review. Carefully defined eligibility criteria inform various steps of the review methodology. They influence the development of the search strategy and serve to ensure that studies are selected in a systematic and unbiased manner."[2] [2] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, et al. (2009) The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLoS Med 6(7): e1000100. doi:10.1371/journal.pmed.1000100	We provided these criteria in the format suggested by the AHRQ Guidelines for AHRQ EPC reports. We believe that our inclusion and exclusion criteria are stated in the Methods section in a clear and transparent format. In addition, we have included our data abstraction forms in an appendix.
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Study Selection criteria	• A list of included studies is requested. While the authors provide excluded studies as part of the report's Appendix, no included studies list is provided. The report notes that 117 studies were included but the reference list at the very end of the document contains 172. It is difficult given the number of studies and the length of the document to match up the included study citations with the studies discussed in the body of the document.	The reference list at the end of the report text lists the 172 studies that were newly identified for the current report (this number includes observational studies identified for the original report and excluded that we have now included). We have now added an appendix that lists the 117 studies that were included in the analyses in the original report, as all of these studies are included in our current analyses.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Study Selection criteria	• Criteria related to study quality are unnecessarily restrictive and likely introduce bias. The current report excluded randomized controlled trials (RCTs) with less than 45 subjects and observational studies with less than 250 participants. Systematic reviews and subsequent meta-analyses are meant to facilitate an evaluation of the totality of the available evidence. The AHRQ ECER Guide notes that excluding studies based on small sample size introduces bias. The Guide provides the following examples: For RCTs - "Reviewer decides to exclude RCTs of less than 50 participants" – For observational studies – "Reviewer decides to exclude… observational studies less than 1000 patients" in both scenarios AHRQ notes - "Exclusion of small studies may exclude valuable information."	We did not exclude any RCTs based on sample size. And small observational studies were excluded only if three or more larger studies were identified AND if the articles were not reporting on analyses of data from a previous trial or a longer term follow-up of an RCT or observational study.
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Study Selection criteria	• Limits to performance of meta-analyses are inconsistent with the prior report and somewhat arbitrary. The report states "We considered meta-analyses when there were at least three trials with similar intervention." The 2005 report was willing to use two studies. There is no precedent in meta-analysis stipulating that three studies must be used and the requirement that the trials be homogenous to start with somewhat undermines the rationale for conducting meta-analyses. The objective of a meta-analysis is to increase statistical power, so a limitation on smaller studies is not necessary and introduces selection bias. If there's concern that smaller studies may suffer from selective reporting, sub-group and sensitivity analysis can and should be run with and without smaller studies and the data presented and discussed.	We realize the original report conducted pooled analyses that included only two studies; however, we made a decision for the current report that we would not conduct pooled analyses of fewer than three studies. Pooled analyses of two studies are subject to a great deal of bias. .

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Study Selection criteria	• Study selection strategies employed in 2005 and 2015 have resulted in a number of studies never being considered as part of the collective evidence base for certain outcomes. In the 2005 report, if an outcome was supported by at least 2 RCTs, AHRQ did not consider observational evidence. In the 2015 report, AHRQ determined that observational data was relevant but elected to exclude "observational studies with enrollment sizes of less than 250 unless no other studies were identified for a particular outcome." In short, some studies were eliminated from consideration in the evidence base twice; once in 2005 for being observational and again in 2015 for having less than 250 subjects. While a few such examples from the gestation length section follow, it's important to note that this does not reflect an exhaustive examination of all outcomes in the report and it's likely that numerous studies were inadvertently excluded from the evidence base as a result of AHRQ's approach: Olsen SF, Hansen HS, Secher NJ, Jensen B, Sandstrom B. Gestation length and birth weight in relation to intake of marine n-3 fatty acids. British Journal of Nutrition. 1995;73(3):397-404. PMID: 7766563. Olsen SF, Hansen HS, Jensen B, Sorensen TI. Pregnancy duration and the ratio of longchain n-3 fatty acids to arachidonic acid in erythrocytes from Faroese women. Journal of Internal Medicine Supplement. 1989;225(731):185-189. PMID: 2706041	Small observational studies were excluded only if three or more larger studies were identified AND if the articles were not reporting on analyses of data from a previous trial or a longer term follow-up of an RCT or observational study. For the current report, we were also tasked with including observational studies that were excluded from the original report because that report identified two or more RCTs that reported on the same outcomes. We screened all such observational studies according to our inclusion and exclusion criteria. A number of the older observational studies were excluded for various reasons, for example the population or intervention did not meet our inclusion criteria). However, only two of the observational studies that were excluded from the original report due to the existence of RCTs on the same outcomes were subsequently excluded again because of small sample size. The outcomes these studies reported were also studied by an exceedingly large number of RCTs and observational studies. One of the two studies was superseded by a longer-term follow-up study, and the other was a study of 18 women from a population of very low applicability to women in the US. The observational studies that were excluded from the original report but subsequently included are listed among the references at the end of the report.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 **Harry B. Rice, PhD** **VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35**	Study Selection criteria	• Fish intake only studies were excluded. The 2010 Dietary Guidelines for Americans[3] acknowledge fish intake as a source of EPA and DHA. "Seafood contributes a range of nutrients, notably the omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)." It further notes that "Moderate evidence indicates that intake of omega-3 fatty acids, in particular DHA, from at least 8 ounces of seafood per week for women who are pregnant or breastfeeding is associated with improved infant health outcomes, such as visual and cognitive development. Therefore, it is recommended that women who are pregnant or breast-feeding consume at least 8 and up to 12 ounces of a variety of seafood per week, from choices that are lower in methyl mercury. Obstetricians and pediatricians should provide guidance to women who are pregnant or breastfeeding to help them make healthy food choices that include seafood." Thus, excluding food-based studies unnecessarily limits the scope of the review and may result in biased conclusions. Notably, this is a shift in inclusion/exclusion criteria from 2005 when intervention/exposure studies investigated foods or supplements that had sources of fatty acids and included fish. If AHRQ is particularly concerned about the heterogeneity introduced by comparing fish and supplements in the same analysis, fish could be analyzed separately. [3]U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2010. 7th Edition, Washington, DC: U.S. Government Printing Office, December 2010.	We stated in the Methods chapter that we excluded studies that assessed associations of fish intake but did not attempt to quantify n-3 FA intake. The meaning of these studies is impossible to interpret and their findings cannot legitimately be compared to the findings of studies with defined intakes of n-3 PUFAs.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Outcome Selection	• Biomarker data was inconsistently used. Biomarker data was not consistently included in all areas of the report. While it is not clear from the inclusion and exclusion criteria, it would appear that for certain outcomes, biomarker data was considered useful but for others it was not. Biomarker studies can provide a better understanding of the mechanisms by which the LCPUFAs provide benefit. Given that our understanding of LCPUFAs continues to evolve and for many outcomes the evidence base remains somewhat limited, exclusion of biomarker data seems premature.	We stated in the Methods that we included any biomarker data that were associated with an outcome of interest. We did not include studies that reported data only on how biomarkers changed in response to interventions or exposures. We included studies that reported associations between biomarker values and outcomes of interest..
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Evaluation of the Totality of Evidence	• Collective analysis of studies identified in 2005 versus 2015 does not consistently occur. The report states that one aim of the 2015 systematic review is "to update the original review on the topic of the effects of n-3 FAs on maternal and child outcomes" and that "new trial results were added to original meta-analyses, when appropriate, based on similarity of participants, interventions (including doses), and outcomes." There is no standard identified for these criteria of addition which may have led to arbitrary addition or exclusion of studies. Moreover, adding to existing meta-analysis was not done consistently. See page 100 of the 2015 report under "Term infant interventions/exposures". This identifies a meta-analysis of "18 good quality studies which had been included in the 2005 report". The additional five studies in the 2015 draft report could have been combined with the earlier meta-analysis, but they weren't. It is unlikely that the heterogeneity of the five new studies is worse than the original 18 thus prohibiting a collective analysis. For this, and other similar outcomes, AHRQ is asked to provide meta-analyses reflecting the total evidence base.	In combining studies identified for the original report with those identified for the current report, we identified a small number of the older studies that were in fact sufficiently heterogeneous compared with the remaining studies that we excluded them from pooled analyses: Therefore we redid those pooled analyses. For example, the original report pooled some studies that enrolled mothers with particular health risks with studies of healthy mothers, where we believed the difference in maternal health risks between studies should not be overlooked.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Evaluation of the Totality of Evidence	• Some Studies were excluded if included in the original report. Appendix Page B-1 begins the list of excluded studies and includes among the reasons "Included in the Original Report-N=32" from 2005. If the totality of the evidence is to be adequately considered, it is unclear why studies considered pertinent in the original report would have been excluded in the update. Examples of key studies excluded for this reason are: Birch EE, Birch DG, Hoffman DR, Uauy R. Dietary essential fatty acid supply and visual acuity development. Invest Ophthalmol Vis Sci. 1992 Oct;33(11):3242-53. Birch EE, Hoffman DR, Castañeda YS, Fawcett SL, Birch DG, Uauy RD. A randomized controlled trial of long-chain polyunsaturated fatty acid supplementation of formula in term infants after weaning at 6 wk of age. Am J Clin Nutr. 2002 Mar;75(3):570-80. Hoffman DR, Birch EE, Birch DG, Uauy R, Castañeda YS, Lapus MG, Wheaton DH. Impact of early dietary intake and blood lipid composition of long-chain polyunsaturated fatty acids on later visual development. J Pediatr Gastroenterol Nutr. 2000 Nov;31(5):540-53. Carlson SE, Werkman SH. A randomized trial of visual attention of preterm infants fed docosahexaenoic acid until two months. Lipids. 1996 1/1996;31(1):85-90. Carlson SE, Werkman SH, Rhodes PG, et al. Visual-acuity development in healthy preterm infants: effect of marine-oil supplementation. American Journal of Clinical Nutrition. 1993 7/1993;58(1):35-42. Note: Both Carlson et al., 1993 and Carlson et al., 1996 were excluded from the original report in 2005 but should have been included in the 2015 draft report.	We have now added an appendix that lists the studies that were included in the original report, most of which we have included in our pooled analyses. The Carlson 1993 study that the commenter notes was not included in the original report was, in fact, included, but the incorrect reference was cited. We are now including the Carlson '96 reference as well.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 **Harry B. Rice, PhD** **VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35**	Evaluation of the Totality of Evidence	[continued from comment above] Smuts CM, Huang M, Mundy D, Plasse T, Major S, Carlson SE. A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. Obstet Gynecol. 2003 Mar;101(3):469-79. **Note:** Two different Smuts et al., 2003 publications were cited in "Figure 6. Incidence of premature birth – DHA vs. placebo" found in the section entitled "Length of Gestation (or Gestational Age) and Preterm Birth", but the full citations were not provided in the "References". In 2003, Smuts et al., published two studies on DHA, including the above cited study. It's not clear how the study cited above could have been excluded (Appendix B-3) and at the same time included (page 23). This is not an isolated mix-up. Despite the massive undertaking, we recommend the draft report be reviewed thoroughly for these types of mistakes. Other examples include the following: Birch et al., 2000 was identified as excluded (Appendix B-1 #5) but was used in the 2015 draft report and cited in the reference list not just once but twice (reference #136 and #137). Additional, random errors were noted in the text and have been listed at the end of our comments. Helland et al., 2001 was identified as excluded (Appendix B-2 #13) but was used in the 2015 draft report (pages 72, 113, 191) and cited in the reference list as #87. Helland et al., 2003 was identified as excluded (Appendix B-2 #14) but was used in the 2015 draft report (pages 27, 46, 56, 66, 67, 72, 85, 113, 160, 178, 191, 211, 212, 227, 228, 248, 249) and cited in the reference list as #52.	We now provide an appendix that lists the studies from the original report that were included. In the first draft of our report, Appendix B listed studies that were identified in our searches but appeared in the original report as excluded. We realize this is confusing and have now created a table that lists the studies from the original report that were included in analyses for the current report. Thank you for pointing out this confusion. We listed the Birch 2000, Helland 2001, and Helland 2003 studies as having been excluded because we found them in our searches but they appeared in the original report; however, we described these studies in our in the report text. Therefore, we have reconfigured the tables of excluded studies. The Birch study was inadvertently entered twice in our database.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Evaluation of the Totality of Evidence	• Conclusions regarding risk of preterm birth failed to consider the evidence from existing meta-analyses, and consideration of sub-analyses. The results of four meta-analyses and two recent large RCTs consistently demonstrate a protective effect of n-3 LCPUFA supplementation during pregnancy, specific to a reduction in incidence of early preterm birth (<34 weeks gestation).[4] Findings from a systematic review[5] and a Cochrane Review6 both suggest positive effects on birth weight and early preterm birth. In the 2006 Cochrane Review[6], infants born to n-3 LCPUFA supplemented mothers were 31% less likely to be born very early (< 34 weeks), and had a higher mean birth weight than controls (mean difference 47g). Even with the inclusion of nine additional trials and different inclusion criteria from the Cochrane Review6, Imhoff-Kunsch[5] also reported a decreased risk of early preterm birth and a higher mean birth weight. References 4 Koletzko B, Boey CC, Campoy C, Carlson SE, Chang N, Guillermo-Tuazon MA, Joshi S, Prell C, Quak SH, Sjarif DR, Su Y, Supapannachart S, Yamashiro Y, Osendarp SJ. Current information and Asian perspectives on long-chain polyunsaturated fatty acids in pregnancy, lactation, and infancy: systematic review and practice recommendations from an early nutrition academy workshop.Ann Nutr Metab. 2014;65(1):49-80. doi: 10.1159/000365767. Epub 2014 Sep 16. Review. 5 Imhoff-Kunsch B, Briggs V, Goldenberg T, Ramakrishnan U Effect of n-3 long-chain polyunsaturated fatty acid intake during pregnancy on maternal, infant, and child health outcomes: a systematic review. Paediatr Perinat Epidemiol. 2012 Jul;26 Suppl 1:91-107. doi: 10.1111/j.1365-3016.2012.01292.x. Review.	We attempted to avoid using existing meta-analyses in our review and have removed the one prior meta-analysis we did include in favor of conducting our own de novo analyses. We verified that we included the studies included in the systematic reviews listed by the commenter that met our inclusion and exclusion criteria and have redone the MA including the newer studies.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35 (continued)	Evaluation of the Totality of Evidence (continued)	6 Makrides M1, Duley L, Olsen SF Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by pre-eclampsia or intrauterine growth restriction. Cochrane Database Syst Rev. 2006 Jul 19;(3):CD003402.	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 **Harry B. Rice, PhD** **VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35**	Evaluation of the Totality of Evidence	Two additional meta-analyses have reported benefits. Horvath et al.[7] reported on high risk pregnancies and Szajewska et al.[8] reported on low risk pregnancies. Although inclusion/exclusion criteria again differed from the Cochrane Review6, both groups arrived at similar conclusions regarding gestation length (<37 weeks) and LBW. Szajewska et al.[8] included six trials (1278 women) and showed LCPUFA supplementation during pregnancy prolonged gestation by 1.57 days (95% CI: 0.35, 2.78 days) with no overall effect on general preterm birth. Horvath et al.[7] with high risk pregnancies, included four studies with 1264 women, did not find a benefit in preterm births < 37 weeks but did for preterm births < 34 weeks gestation (RR 0.99; 95% CI: 0.9, 1.1). None of these meta-analyses included Carlson et al., 2013[9] which reported a reduction in early preterm birth of 4.8% in the control group compared to 0.6% in the intervention group (p=0.026). The effect sizes were 26% in the most recent meta-analysis, and 51% and 87.5%, respectively in two more recent large RCTs using higher n-3 LCPUFA dosages (600[9] or 800[10] mg/day). References: 7 Horvath A, Koletzko B, Szajewska H. Effect of supplementation of women in high-risk pregnancies with long-chain polyunsaturated fatty acids on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials. Br J Nutr. 2007 Aug;98(2):253-9. Epub 2007 Apr 10.	We have now briefly addressed the similarities and differences between our findings and those of these reviews in our Discussion. We too find an increase in gestational length but not in risk for preterm birth. We believe several factors may account for this apparent divergence, e.g., studies that assessed effects of gestational length often excluded infants born preterm; and the observed effect size for increase in gestational length was likely too small to translate to a meaningful decrease in the risk for preterm birth. Having said that, any differences between our findings and those of earlier meta-analyses could also be due to the fact that we use the Hartung-Knapp-Sidik-Jonkman method of random effects meta-analysis, as is now mandated, and it is a less forgiving method than the traditional derSimonian and Laird method.

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Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35 (continued)	Evaluation of the Totality of Evidence (continued)	8 Szajewska H, Horvath A, Koletzko B. Effect of n-3 long-chain polyunsaturated fatty acid supplementation of women with low-risk pregnancies on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2006 Jun;83(6):1337-44. Review 9 Carlson SE, Colombo J, Gajewski BJ, Gustafson KM, Mundy D, Yeast J, Georgieff MK, Markley LA, Kerling EH, Shaddy DJ. DHA supplementation and pregnancy outcomes. Am J Clin Nutr. 2013 Apr;97(4):808-15. doi: 10.3945/ajcn.112.050021. Epub 2013 Feb 20 10 Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P; DOMInO Investigative Team. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. JAMA. 2010 Oct 20;304(15):1675-83. doi: 10.1001/jama.2010.1507	
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Noted errors in the text	The following errors were found in the text of the draft report: • The section entitled “Infant Formula Supplementation with n-3 FA and Visual Acuity in Preterm infants”, which begins on page 171, addresses cognition, not visual acuity. The same section title is used beginning on page 154. The difference is that the information under the section title beginning on page 154 addresses visual acuity. Visual acuity is addressed on pages 151-168.	We have corrected the error in the title of the section

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Noted errors in the text	• The section entitled "Infant Formula Supplementation with n-3 FA and Visual Acuity in Full Term infants", which begins on page 172, addresses cognition, not visual acuity. A similar section title "Infant Formula Supplementation with n-3 FA and Visual Acuity in Term Infants" is used beginning on page 155. The difference is that the information under the section title beginning on page 155 addresses visual acuity. Visual acuity is addressed on pages 151-168.	We have corrected the error in the text.
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Noted errors in the text	• Reference #131 cited on page 153 under the section on vision is not a vision study.	We have corrected the error in the text.
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Noted errors in the text	• On page ES-9, under "Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes" the AHRQ Methods guide is cited as reference #4, but it's #9 in the reference list.	We have corrected the error in the text.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Noted errors in the text	• The section on "Allergies" (page 220) states a total of ten RCTs and six observational studies were included, but there are only nine RCTs and 12 observational studies included in the evidence tables.	We have corrected the error in the text.
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Noted errors in the text	• The section on "Atopic Dermatitis and Eczema" (page 204) states a total of ten observational studies were included, but there are only seven observational studies included in the evidence table.	We have corrected the error in the text.
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Conclusions	Based on the gap between the findings of the current draft report and previous systematic reviews and meta-analyses, it is uncertain if the current report adequately explored the evidence base, for example, by considering sub-analyses to look at early preterm birth. Early preterm birth and birth weight are risk factors for increased morbidity and mortality. Global health organizations have identified the need to reduce the risk of preterm birth and early preterm birth.	We re-reviewed the studies identified for the original report as well as the current report and were unable to identify more than 1 or two that assessed the incidence of early preterm birth, e.g., Carlson et al., 2013, which we included.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 Harry B. Rice, PhD VP, Reg. & Scientific Affairs Global Organization for EPA and DHA Omega-35	Conclusions	GOED submitted comments concerning the draft report entitled “Omega-3 Fatty Acids and Cardiovascular Disease: An Updated Systematic Review” by the due date of August 31, 2015. Given the public health implications, GOED encourages you to confirm that draft report does not lack the same rigor found in the current report. If you have any questions, please do not hesitate to contact me at harry@goedomega3.com or 763-391-7641.	We have conducted an update search, incorporated numerous additional studies, and entirely reanalyzed most of the data in the draft report. We stand behind the current report and its conclusions.