



United States Department of Agriculture

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# **Omega-3 fatty acids from Supplements Consumed before and during Pregnancy and Lactation and Developmental Milestones, Including Neurocognitive Development, in the Child: A Systematic Review**

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2020 Dietary Guidelines Advisory Committee,  
Pregnancy and Lactation Subcommittee

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Nutrition Evidence Systematic Review  
Center for Nutrition Policy and Promotion  
Food and Nutrition Service  
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This systematic review was conducted by the 2020 Dietary Guidelines Advisory Committee in collaboration with the Nutrition Evidence Systematic Review (NESR) team at the Center for Nutrition Policy and Promotion, Food and Nutrition Service, U.S. Department of Agriculture (USDA). All systematic reviews from the 2020 Advisory Committee Project are available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews>.

Conclusion statements drawn as part of this systematic review describe the state of science related to the specific question examined. Conclusion statements do not draw implications, and should not be interpreted as dietary guidance. This portfolio provides the complete documentation for this systematic review. A summary of this review is included in the 2020 Advisory Committee's Scientific Report available at [www.DietaryGuidelines.gov](http://www.DietaryGuidelines.gov).

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USDA and HHS implemented a process to identify topics and scientific questions to be examined by the 2020 Dietary Guidelines Advisory Committee. The Committee conducted its review of evidence in subcommittees for discussion by the full Committee during its public meetings. The role of the Committee members involved establishing all aspects of the protocol, which presented the plan for how they would examine the scientific evidence, including the inclusion and exclusion criteria; reviewing all studies that met the criteria they set; deliberating on the body of evidence

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<sup>i</sup> Under contract with the Food and Nutrition Service, United States Department of Agriculture.

for each question; and writing and grading the conclusion statements to be included in the scientific report the 2020 Committee submitted to USDA and HHS. The NESR team with assistance from Federal Liaisons and Project Leadership, supported the Committee by facilitating, executing, and documenting the work necessary to ensure the reviews were completed in accordance with NESR methodology. More information about the 2020 Dietary Guidelines Advisory Committee, including the process used to identify topics and questions, can be found at [www.DietaryGuidelines.gov](http://www.DietaryGuidelines.gov). More information about NESR can be found at [NESR.usda.gov](http://NESR.usda.gov).

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## INTRODUCTION

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This document describes a systematic review conducted to answer the following question: What is the relationship between omega-3 fatty acid supplements consumed before and during pregnancy and lactation and developmental milestones, including neurocognitive development, in the child? This systematic review was conducted by the 2020 Dietary Guidelines Advisory Committee, supported by USDA's Nutrition Evidence Systematic Review (NESR).

More information about the 2020 Dietary Guidelines Advisory Committee is available at the following website: [www.DietaryGuidelines.gov](http://www.DietaryGuidelines.gov).

NESR specializes in conducting food- and nutrition-related systematic reviews using a rigorous, protocol-driven methodology. More information about NESR is available at the following website: [NESR.usda.gov](http://NESR.usda.gov).

NESR's systematic review methodology involves developing a protocol, searching for and selecting studies, extracting data from and assessing the risk of bias of each included study, synthesizing the evidence, developing conclusion statements, grading the evidence underlying the conclusion statements, and recommending future research. A detailed description of the systematic reviews conducted for the 2020 Dietary Guidelines Advisory Committee, including information about methodology, is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews>. In addition, starting on page 84, this document describes the final protocol as it was applied in the systematic review. A description of and rationale for modifications made to the protocol are described in the 2020 Dietary Guidelines Advisory Committee Report, Part D: Chapter 2. Food, Beverage, and Nutrient Consumption During Pregnancy and Chapter 3. Food, Beverage, and Nutrient Consumption During Lactation.

## List of abbreviations

<b>Abbreviation</b>	<b>Full name</b>
ADD	Attention deficit disorder
ADHD	Attention-deficit/hyperactivity disorder
ARA	Arachidonic acid
ASD	Autism spectrum disorder
CNPP	Center for Nutrition Policy and Promotion
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
FNS	Food and Nutrition Service
HHS	Department of Health and Human Services
MTHF	Methyl tetrahydrofolate
NESR	Nutrition Evidence Systematic Review
NIH	National Institutes of Health
RCT	Randomized controlled trial
PCS	Prospective cohort study
USDA	United States Department of Agriculture
WASI	Wechsler Abbreviated Scale of Intelligence
WISC	Wechsler Intelligence Scale for Children
WPPSI	Wechsler Primary and Preschool Scale of Intelligence

# WHAT IS THE RELATIONSHIP BETWEEN OMEGA-3 FATTY ACID SUPPLEMENTS CONSUMED BEFORE AND DURING PREGNANCY AND LACTATION AND DEVELOPMENTAL MILESTONES, INCLUDING NEUROCOGNITIVE DEVELOPMENT, IN THE CHILD?

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## PLAIN LANGUAGE SUMMARY

### What is the question?

- The question is: What is the relationship between omega-3 fatty acid supplements consumed before and during pregnancy and lactation and developmental milestones, including neurocognitive development, in the child?

### What is the answer to the question?

#### *Pregnancy*

- Limited evidence suggests that omega-3 fatty acid supplementation during pregnancy may result in favorable cognitive development in the child.
- Insufficient evidence is available to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation, or during pregnancy only, and language and social emotional development in the child.
- Insufficient evidence is available to determine the relationship between omega-3 fatty acid supplementation during pregnancy and motor and visual development, academic performance, and the risk of attention-deficit disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorder in the child.
- No evidence is available to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation, or during pregnancy only, and anxiety or depression in the child.
- Insufficient evidence is available to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation and cognitive development in the child.
- No evidence is available to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation and visual development, academic performance, or the risk of attention-deficit disorder, attention-deficit/hyperactivity disorder, or autism spectrum disorder in the child.

#### *Lactation*

- Insufficient evidence is available to determine the relationship between omega-3 fatty acid supplementation consumed during both pregnancy and lactation or during lactation alone, and cognitive, language, motor, and visual development in the child.
- No evidence is available to determine the relationship between omega-3 fatty acid supplementation consumed during both pregnancy and lactation or during lactation alone and academic performance, anxiety, depression, or the risk of attention-deficit disorder, attention-deficit/hyperactivity disorder, or autism spectrum disorder in the child.
- No evidence is available to determine the relationship between omega-3 fatty acid

supplementation consumed during lactation and social-emotional development in the child.

### **Why was this question asked?**

- This important public health question was identified by the U.S. Departments of Agriculture (USDA) and Health and Human Services (HHS) to be examined by the 2020 Dietary Guidelines Advisory Committee.

### **How was this question answered?**

- The 2020 Dietary Guidelines Advisory Committee, Pregnancy and Lactation Subcommittee conducted a systematic review to answer this question with support from the Nutrition Evidence Systematic Review (NESR) team.

### **What is the population of interest?**

- For the intervention/exposure, generally healthy women before and/or during pregnancy and lactation.
- For the outcome, infants and toddlers (birth to 24 months) and children and adolescents (ages 2-18 years).

### **What evidence was found?**

- This systematic review includes 33 articles that present evidence about omega-3 fatty acid supplementation during pregnancy alone (25 articles), during both pregnancy and lactation (6 articles), or during lactation alone (2 articles).
- Most of the evidence is about cognitive development in children. Generally, omega-3 fatty acid supplementation during pregnancy alone had either no effect or a beneficial effect on child cognitive development. Although the evidence is based on studies with a strong design (randomized controlled trials), the results were somewhat inconsistent across the different measures of child cognitive development.
- Due to inconsistent results, a conclusion could not be drawn on the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation or during lactation alone and cognitive development in children.
- Due to inconsistent results or an insufficient number of studies, a conclusion could not be drawn on the relationship between omega-3 fatty acid supplementation and language, motor, visual, and social-emotional development; academic performance, anxiety, and depression; and the risk of attention-deficit disorder (ADD), attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD).

### **How up-to-date is this systematic review?**

- This review searched for studies from January 1980 to February 2020.

# TECHNICAL ABSTRACT

## Background

- This important public health question was identified by the U.S. Departments of Agriculture (USDA) and Health and Human Services (HHS) to be examined by the 2020 Dietary Guidelines Advisory Committee.
- The 2020 Dietary Guidelines Advisory Committee, Pregnancy and Lactation Subcommittee conducted a systematic review to answer this question with support from the Nutrition Evidence Systematic Review (NESR) team.
- The goal of this systematic review was to examine the following question: What is the relationship between omega-3 fatty acid supplements consumed before and during pregnancy and lactation and developmental milestones, including neurocognitive development, in the child?

## Conclusion statements and grades

- **Pregnancy**
  - Limited evidence suggests that omega-3 fatty acid supplementation during pregnancy may result in favorable cognitive development in the child. (Grade: Limited)
  - Insufficient evidence is available to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation, or during pregnancy only, and language and social emotional development in the child. (Grade: Grade not assignable)
  - Insufficient evidence is available to determine the relationship between omega-3 fatty acid supplementation during pregnancy and motor and visual development, academic performance, and the risk of attention-deficit disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorder in the child. (Grade: Grade not assignable)
  - No evidence is available to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation, or during pregnancy only, and anxiety or depression in the child. (Grade: Grade not assignable)
  - Insufficient evidence is available to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation and cognitive development in the child. (Grade: Grade not assignable)
  - No evidence is available to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation and visual development, academic performance, or the risk of attention-deficit disorder, attention-deficit/hyperactivity disorder, or autism spectrum disorder in the child. (Grade: Grade not assignable)
- **Lactation**
  - Insufficient evidence is available to determine the relationship between omega-3 fatty acid supplementation consumed during both pregnancy and lactation or during lactation alone, and cognitive, language, motor, and visual development in the child. (Grade: Grade not assignable)
  - No evidence is available to determine the relationship between omega-3

fatty acid supplementation consumed during both pregnancy and lactation or during lactation alone and academic performance, anxiety, depression, or the risk of attention-deficit disorder, attention-deficit/hyperactivity disorder, or autism spectrum disorder in the child. (Grade: Grade not assignable)

- No evidence is available to determine the relationship between omega-3 fatty acid supplementation consumed during lactation and social-emotional development in the child. (Grade: Grade not assignable)

## Methods

- Literature search was conducted using 4 databases (PubMed, Cochrane, Embase, and CINAHL) to identify articles that evaluated an intervention or exposure of omega-3 fatty acid supplements consumed before and during pregnancy and/or lactation and the outcome of developmental milestones, including neurocognitive development, in the child. A manual search was also conducted to identify articles that may not have been included in the electronic databases searched. Articles were screened by two NESR analysts independently for inclusion based on pre-determined criteria.
- Data extraction and risk of bias assessment were conducted for each included study, and both were checked for accuracy. The Committee qualitatively synthesized the body of evidence to inform development of a conclusion statement(s), and graded the strength of evidence using pre-established criteria for risk of bias, consistency, directness, precision, and generalizability.

## Summary of the evidence

### ***Pregnancy only, and both pregnancy and lactation***

- This systematic review included 31 articles from 14 randomized controlled trials (RCTs) and 1 prospective cohort study (PCS) published between 1980 and 2020.
- Studies included in this review assessed interventions/exposures during:
  - Pregnancy only: 11 RCTs (24 articles); 1 PCS (1 article)
  - Both pregnancy and lactation: 3 RCTs (6 articles)
- 11 of the 14 RCTs assessed cognitive development
  - Eight RCTs delivered omega-3 fatty acid supplements during pregnancy alone. Of those 8 RCTs, 5 studies (11 articles) reported at least one statistically significant finding that supplementation resulted in favorable cognitive development in the child. One study reported at least one statistically significant finding that supplementation resulted in unfavorable measures of cognitive development in the child. All 8 studies reported at least one statistically non-significant result. Overall, results were inconsistent across different measures both within and between studies.
  - Three RCTs delivered omega-3 fatty acid supplements during both pregnancy and lactation. Of those 3 RCTs, 1 study reported at least one statistically significant finding that supplementation resulted in favorable cognitive development in the child. All 3 studies reported at least one statistically non-significant result.
- For language, motor, visual, and social-emotional development, findings were inconsistent and therefore a conclusion statement could not be drawn. Although all studies reported at least one statistically non-significant result, the number and direction of statistically significant findings varied across the body of evidence.

- Only 1 study examined academic performance; therefore, a conclusion could not be drawn.
- No evidence was available on omega-3 fatty acid supplementation and anxiety or depression.
- Only 1 study (2 articles) assessed the risk of attention-deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD); therefore a conclusion could not be drawn.
- Only 1 RCT and 1 PCS study assessed risk of autism spectrum disorder (ASD), and both had methodological limitations; therefore, the evidence was deemed insufficient to draw a conclusion.
- The ability to draw strong conclusions was limited by the following issues:
  - Wide variation in the developmental domains assessed, as well as in the measures used to evaluate child performance in each of those domains, which limited the ability to compare results across studies.
  - Potential risk of bias due to missing outcome data. Further, a lack of pre-registered data analysis plans potentially increased the risk of bias due to selectivity in results presented.
  - Findings were mixed both within and between studies, and these inconsistencies could not be explained by methodological differences.
  - Although some studies published results from multiple follow-up assessments, an insufficient number of studies were available to investigate the relationship between omega-3 fatty acid supplementation and developmental milestones in the child for many exposure-outcome pairs. Additionally, several studies did not provide evidence of sufficient sample size to detect effects, either because the study did not achieve the required sample size estimated by power calculations or because the study did not report a power calculation. This is particularly true for the long-term outcome assessments.
  - People with lower socioeconomic status, adolescents, and racially and ethnically diverse populations were underrepresented in the body of evidence.

### ***Lactation only, and both pregnancy and lactation***

- This systematic review included 8 articles from 4 RCTs published between 1980 and 2020.
- Studies included in this review assessed interventions/exposures during:
  - Both pregnancy and lactation: 3 RCTs (6 articles)
  - Lactation alone: 1 RCT (2 articles)
- All 4 RCTs assessed cognitive development
  - Three RCTs provided omega-3 fatty acid supplements during both pregnancy and lactation. Of those 3 RCTs, 1 study reported at least one statistically significant finding that supplementation resulted in favorable cognitive development in the child. All 3 studies reported at least one statistically non-significant result.
  - One RCT provided omega-3 fatty acid supplements during lactation alone and showed a benefit of supplementation on one measure of cognitive development in the child. The study also reported statistically non-significant results on other measures of cognitive development.
- For language, motor, and social-emotional development, findings were inconsistent and therefore a conclusion statement could not be drawn. Although all studies

reported at least one statistically non-significant result, the number and direction of statistically significant findings varied across the body of evidence.

- No evidence was available on omega-3 fatty acid supplementation and visual development, academic performance, anxiety, depression or the risk of ADD, ADHD, or ASD.
- The ability to draw strong conclusions was limited by the following issues:
  - Wide variation in the developmental domains assessed, as well as in the measures used to evaluate child performance in each of those domains, limited the ability to compare results across studies.
  - Missing outcome data raised concerns about risk of bias. Further, a lack of preregistered data analysis plans potentially increased the risk of bias due to selectivity in results presented.
  - Findings were mixed both within and between studies, and these inconsistencies could not be explained by methodological differences.
  - Although some studies published results from multiple follow-up assessments, an insufficient number of studies were available to investigate the relationship between omega-3 fatty acid supplementation and developmental milestones in the child for many exposure-outcome pairs. Additionally, multiple studies did not provide evidence of sufficient sample size to detect effects, either because the study did not achieve the required sample size estimated by power calculations or because the study did not report a power calculation. This is particularly true for the long-term outcome assessments.
  - People with lower socioeconomic status, adolescents, and racially and ethnically diverse populations were underrepresented in the body of evidence.

## **FULL REVIEW**

### **Systematic review question**

What is the relationship between omega-3 fatty acids from supplements consumed before and during pregnancy and lactation and developmental milestones, including neurocognitive development, in the child?

### **Conclusion statements and grades**

#### **Pregnancy**

Limited evidence suggests that omega-3 fatty acid supplementation during pregnancy may result in favorable cognitive development in the child. (Grade: Limited)

Insufficient evidence is available to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation, or during pregnancy only, and language and social emotional development in the child. (Grade: Grade not assignable)

Insufficient evidence is available to determine the relationship between omega-3 fatty acid supplementation during pregnancy and motor and visual development, academic performance, and the risk of attention-deficit disorder, attention-deficit/hyperactivity disorder, and autism spectrum disorder in the child. (Grade: Grade not assignable)

No evidence is available to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation, or during pregnancy only, and anxiety or depression in the child. (Grade: Grade not assignable)

Insufficient evidence is available to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation and cognitive development in the child. (Grade: Grade not assignable)

No evidence is available to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation and visual development, academic performance, or the risk of attention-deficit disorder, attention-deficit/hyperactivity disorder, or autism spectrum disorder in the child. (Grade: Grade not assignable)

#### **Lactation**

Insufficient evidence is available to determine the relationship between omega-3 fatty acid supplementation consumed during both pregnancy and lactation or during lactation alone, and cognitive, language, motor, and visual development in the child. (Grade: Grade not assignable)

No evidence is available to determine the relationship between omega-3 fatty acid supplementation consumed during both pregnancy and lactation or during lactation alone and academic performance, anxiety, depression, or the risk of attention-deficit disorder, attention-deficit/hyperactivity disorder, or autism spectrum disorder in the child. (Grade: Grade not assignable)

No evidence is available to determine the relationship between omega-3 fatty acid supplementation consumed during lactation and social-emotional development in the child. (Grade: Grade not assignable)

## Summary of the evidence

### *Pregnancy only, and both pregnancy and lactation*

- This systematic review included 31 articles from 14 RCTs and 1 PCS published between 1980 and 2020.<sup>1-31</sup>
- Studies included in this review assessed interventions/exposures during:
  - Pregnancy only: 11 RCTs (24 articles); 1 PCS (1 article)
  - Both pregnancy and lactation: 3 RCTs (6 articles)
- 11 of the 14 RCTs assessed cognitive development
  - Eight RCTs delivered omega-3 fatty acid supplements during pregnancy alone. Of those 8 RCTs, 5 studies (11 articles) reported at least one statistically significant finding that supplementation resulted in favorable cognitive development in the child. One study reported at least one statistically significant finding that supplementation resulted in unfavorable measures of cognitive development in the child. All 8 studies reported at least one statistically non-significant result. Overall, results were inconsistent across different measures both within and between studies.
  - Three RCTs delivered omega-3 fatty acid supplements during both pregnancy and lactation. Of those 3 RCTs, 1 study reported at least one statistically significant finding that supplementation resulted in favorable cognitive development in the child. All 3 studies reported at least one statistically non-significant result.
- For language, motor, visual, and social-emotional development, findings were inconsistent and therefore a conclusion statement could not be drawn. Although all studies reported at least one statistically non-significant result, the number and direction of statistically significant findings varied across the body of evidence.
- Only 1 study examined academic performance; therefore, a conclusion could not be drawn.
- No evidence was available on omega-3 fatty acid supplementation and anxiety or depression.
- Only 1 study (2 articles) assessed the risk of attention-deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD); therefore a conclusion could not be drawn.
- Only 1 RCT and 1 PCS study assessed risk of autism spectrum disorder (ASD), and both had methodological limitations; therefore, the evidence was deemed insufficient to draw a conclusion.
- The ability to draw strong conclusions was limited by the following issues:
  - Wide variation in the developmental domains assessed, as well as in the measures used to evaluate child performance in each of those domains, which limited the ability to compare results across studies.
  - Potential risk of bias due to missing outcome data. Further, a lack of pre-registered data analysis plans potentially increased the risk of bias due to

- selectivity in results presented.
- Findings were mixed both within and between studies, and these inconsistencies could not be explained by methodological differences.
- Although some studies published results from multiple follow-up assessments, an insufficient number of studies were available to investigate the relationship between omega-3 fatty acid supplementation and developmental milestones in the child for many exposure-outcome pairs. Additionally, several studies did not provide evidence of sufficient sample size to detect effects, either because the study did not achieve the required sample size estimated by power calculations or because the study did not report a power calculation. This is particularly true for the long-term outcome assessments.
- People with lower socioeconomic status, adolescents, and racially and ethnically diverse populations were underrepresented in the body of evidence.

### ***Lactation only, and both pregnancy and lactation***

- This systematic review included 8 articles from 4 RCTs published between 1980 and 2020.<sup>1,13-15,30-33</sup>
- Studies included in this review assessed interventions and exposures during:
  - Both pregnancy and lactation: 3 RCTs (6 articles)
  - Lactation alone: 1 RCT (2 articles)
- All 4 RCTs assessed cognitive development:
  - Three RCTs provided omega-3 fatty acid supplements during both pregnancy and lactation. Of those 3 RCTs, 1 study reported at least one statistically significant finding that supplementation resulted in favorable cognitive development in the child. All 3 studies reported at least one statistically non-significant result.
  - One RCT provided omega-3 fatty acid supplements during lactation alone and showed a benefit of supplementation on one measure of cognitive development in the child. The study also reported statistically non-significant results on other measures of cognitive development.
- For language, motor, and social-emotional development, findings were inconsistent and therefore a conclusion statement could not be drawn. Although all studies reported at least one statistically non-significant result, the number and direction of statistically significant findings varied across the body of evidence.
- No evidence was available on omega-3 fatty acid supplementation and visual development, academic performance, anxiety, depression or the risk of ADD, ADHD, or ASD.
- The ability to draw strong conclusions was limited by the following issues:
  - Wide variation in the developmental domains assessed, as well as in the measures used to evaluate child performance in each of those domains, limited the ability to compare results across studies.
  - Missing outcome data raised concerns about risk of bias. Further, a lack of preregistered data analysis plans potentially increased the risk of bias due to selectivity in results presented.
  - Findings were mixed both within and between studies, and these inconsistencies could not be explained by methodological differences.
  - Although some studies published results from multiple follow-up assessments, an insufficient number of studies were available to investigate the relationship

between omega-3 fatty acid supplementation and developmental milestones in the child for many exposure-outcome pairs. Additionally, multiple studies did not provide evidence of sufficient sample size to detect effects, either because the study did not achieve the required sample size estimated by power calculations or because the study did not report a power calculation. This is particularly true for the long-term outcome assessments.

- People with lower socioeconomic status, adolescents, and racially and ethnically diverse populations were underrepresented in the body of evidence.

## Description of the evidence

This systematic review included articles that address the relationship between omega-3 fatty acid supplements<sup>ii</sup> consumed before or during pregnancy and/or lactation and developmental milestones, including neurocognitive development, in the child. The search included articles from very high and high Human Development Index<sup>iii</sup> countries and the search timeframe spanned from January 1980 to February 2020. Studies included generally healthy women before and/or during pregnancy and lactation. The following study designs were included: RCTs, non-randomized controlled trials, prospective and retrospective cohort studies and nested case-control studies.

This body of evidence includes 33 articles from 16 studies, including 15 RCTs<sup>1-15,17-33</sup> and 1 PCS.<sup>16</sup> References are included for each study in Table 1 with trial/cohort names or locations when names were unavailable.

Five of the 16 studies were conducted in the United States.<sup>5,6,12,16,18,32,33</sup> In addition, 2 studies each were conducted in Australia,<sup>7,9-11,19,20,22,28</sup> Canada,<sup>17,23,24</sup> and Germany,<sup>1-4,8</sup> and 1 each in Hungary,<sup>2,3,8</sup> Iran,<sup>25</sup> Mexico,<sup>26,27,29</sup> the Netherlands,<sup>30,31</sup> Norway,<sup>13-15</sup> Spain,<sup>2-4,8</sup> and the United Kingdom.<sup>21</sup>

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<sup>ii</sup> *Dietary supplement* was defined as a product (other than tobacco) that: is intended to supplement the diet; contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement (ODS; Dietary Supplement Health and Education Act, 1994). *Fortification* was defined as the deliberate addition of one or more essential nutrients to a food, whether or not it is normally contained in the food (FDA).

<sup>iii</sup> The Human Development classification was based on the Human Development Index (HDI) ranking from the year the study intervention occurred or data were collected (UN Development Program. HDI 1990-2017 HDRO calculations based on data from UNDESA (2017a), UNESCO Institute for Statistics (2018), United Nations Statistics Division (2018b), World Bank (2018b), Barro and Lee (2016) and IMF (2018). Available from: <http://hdr.undp.org/en/data>). If the study did not report the year in which the intervention occurred or data were collected, the HDI classification for the year of publication was applied. HDI values are available from 1980, and then from 1990 to present. If a study was conducted prior to 1990, the HDI classification from 1990 was applied. When a country was not included in the HDI ranking, the current country classification from the World Bank was used instead (The World Bank. World Bank country and lending groups. Available from: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-country-and-lending-groups>).

**Table 1. Included trials and cohorts**

<b>Trial/Cohort name</b>	<b>Reference numbers for included article</b>
<b>Randomized controlled trials</b>	
<b>DOMInO trial<sup>iv</sup></b>	9-11,19,20,28
<b>KUDOS<sup>iv</sup></b>	5,6
<b>NUHEAL<sup>iv</sup></b>	2-4,8
<b>POSGRAD</b>	26,27,29
<b>Oslo (Norway)</b>	13-15
<b>Gronigen (Netherlands)</b>	30,31
<b>Houston (USA)</b>	32,33
<b>Perth (Australia)</b>	7,22
<b>Vancouver (Canada) <i>Mulder et al</i></b>	23,24
<b>Pittsburgh (USA)</b>	18
<b>Tabriz (Iran)</b>	25
<b>INFAT</b>	1
<b>Vancouver (Canada) <i>Innis and Friesen</i></b>	17
<b>Glasgow (UK)</b>	21
<b>Kansas City (USA)</b>	12
<b>Prospective Cohort Studies</b>	
<b>MARBLES<sup>iv</sup></b>	16

**Participant characteristics:**

- Sample size of the RCTs ranged from 44<sup>12</sup> to 900 participants,<sup>29</sup> and the PCS included 258 participants.<sup>16</sup>
- All of the studies were conducted predominantly in adult women (mean age ~26-34 years) who had singleton pregnancies.

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<sup>iv</sup> DOMInO: DHA to Optimize Mother Infant Outcome; INFAT: The Impact of the Nutritional Fatty Acids During Pregnancy and Lactation for Early Human Adipose Tissue Development; KUDOS: Kansas University DHA Outcomes Study; MARBLES: Markers of Autism Risk in Babies-Learning Early Signs; NUHEAL: Nutraceuticals for a Healthier Life; POSGRAD: Prenatal Omega 3 Supplementation on child Growth and Development

- Race/ethnicity: Six of the 16 studies noted that the participants were predominantly or exclusively White.<sup>7,10,11,16,17,19,22-24,32,33</sup> Catena et al<sup>3</sup> reported that 100 percent of the children in the follow-up were White. One study exclusively included mothers from Mexico,<sup>26,27,29</sup> and another exclusively included Black women.<sup>18</sup> Ostadrahimi et al<sup>25</sup> exclusively recruited Iranian women. Six percent and 31 percent of participants identified as Hispanic or Black, respectively, in the Colombo et al study.<sup>5,6</sup> The Gustafson et al study<sup>12</sup> reported the following on race/ethnicity: 37.3 percent Black, 46.3 percent White, 13.4 percent Hispanic, and 3 percent Asian. Five studies did not report race/ethnicity.<sup>1,9-11,13-15,19-21,30,31</sup>
- Socio-economic status
  - Maternal education:
    - A majority of the studies reported that the participants had at least some college education, on average.<sup>1,5-7,9-17,19,20,22-24,26-33</sup>
    - Four studies did not report maternal education.<sup>18,21</sup>
  - Income: Two studies included predominantly<sup>5,6</sup> or exclusively<sup>18</sup> women with low or middle incomes and 2 studies<sup>3,17</sup> reported that >75 percent of participants had middle or high incomes. In 1 study nearly 20 percent of participants reported insufficient income.<sup>25</sup> The remaining studies did not report income.

## Intervention/Exposures

### ***Supplement dose and composition***

- Seven RCTs provided docosahexaenoic acid (DHA),<sup>5,6,12,17,21,23,24,26,27,29,32,33</sup> 4 RCTs provided both DHA and eicosapentaenoic acid (EPA),<sup>1-4,7-11,19,20,22,25,28,30,31</sup> and 1 RCT was a 2x2 trial of DHA and arachidonic acid (ARA).<sup>30,31</sup> In addition to DHA and EPA, Keenan et al<sup>18</sup> also provided 40 mg/d docosapentaenoic and 90 mg/d eicosatetraenoic acids. Helland et al<sup>13-15</sup> provided 10 mL/d cod liver oil.
  - DHA dose ranged from 120 mg/d to 2.2 g/d and EPA dose ranged from 100 mg/d to 1.1 g/d.
- Most of the RCTs included a placebo composed of corn oil,<sup>13-15</sup> soybean oil,<sup>30,31</sup> or both.<sup>5,6,12,17,23,24,26,27,29,32,33</sup> Keenan et al<sup>18</sup> included a placebo of soybean oil combined with vitamin E and small amounts of DHA and EPA. Placebos in other studies contained sunflower oil alone<sup>21</sup> or in combination with rapeseed and palm oils,<sup>9-11,19,28</sup> olive oil,<sup>7,22</sup> or liquid paraffin.<sup>25</sup> One study included only the vitamins and minerals also included in the intervention supplement, minus DHA, EPA, and 5-MTHF.<sup>2-4</sup> Brei et al<sup>1</sup> did not include a placebo, but the control group received general information about a healthy diet.
- The PCS by Huang et al<sup>16</sup> examined omega-3 fatty acid supplementation dose as a continuous variable, but did not specify supplement composition.

### ***Timing of exposure***

- Studies included in this review assessed interventions/exposures during:
  - Pregnancy alone: 11 RCTs<sup>2-12,17-31</sup> provided supplements from some point during the second trimester through delivery with one exception: Keenan et al<sup>18</sup> provided supplements from week 16-20 of gestation and continued for 6 weeks (i.e., provided omega-3 fatty acid supplements only during second

trimester). One PCS assessed omega-3 fatty acid supplement intake throughout pregnancy.<sup>16</sup>

- Both pregnancy and lactation: Three RCTs provided supplements from the second trimester of pregnancy through 3 months<sup>13-15,30,31</sup> or 4 months postpartum.<sup>1</sup>
- Lactation alone: One RCT provided supplements from 5 days after birth through 4 months postpartum.<sup>32,33</sup>

## Outcome

### ***Cognitive development***

- 12 RCTs assessed cognitive development, using measures of intelligence, attention, executive function, and information processing speed, as well as more general or comprehensive measures (see **Table 2** for details). Of those 12 studies, 8 provided omega-3 fatty acid supplements during pregnancy alone,<sup>2,4-7,9-12,19,22-27,29</sup> 3 during both pregnancy and lactation,<sup>1,13-15,31</sup> and 1 during lactation alone.<sup>32,33</sup>
- The timing of cognitive development assessment in the children ranged from the neonatal period to 10 years, with the following distribution:
  - Birth to 12 months: 8 RCTs<sup>5,12,13,22,24,25,29,33</sup>
  - >12 months to 2 years: 5 RCTs<sup>6,9,10,19,24,27,31</sup>
  - >2 years to 5 years: 7 RCTs<sup>1,6,7,9,10,15,26,32,33</sup>
  - >5 years: 5 RCTs<sup>2,4,6,11,14,23</sup>

### ***Language development***

- Nine RCTs assessed language development (see **Table 3**). Of those 9, 7 provided omega-3 fatty acid supplements during pregnancy alone,<sup>6,7,9-11,18,19,22,23,25,26</sup> 1 during both pregnancy and lactation,<sup>1</sup> and 1 during lactation alone.<sup>33</sup>
- The timing of language development assessment in the children ranged from 3 months to 12 years postpartum, with the following distributions:
  - Birth to 12 months: 4 RCTs<sup>18,23,25,33</sup>
  - >12 months to 2 years: 3 RCTs<sup>6,9,19,23</sup>
  - >2 years to 5 years: 6 RCTs<sup>1,6,7,10,26,33</sup>
  - >5 years: 3 RCTs<sup>11,22,23</sup>

### ***Motor development***

- Ten RCTs assessed motor development, including measures of gross and fine motor function (detailed in **Table 4**). Of those 10, 7 provided omega-3 fatty acid supplements during pregnancy alone,<sup>2,12,18,19,24-27</sup> 2 during both pregnancy and lactation,<sup>1,30,31</sup> and 1 during lactation alone.<sup>32,33</sup>
- The timing of motor development assessment in the children ranged from 1 week to 5.5 years postpartum, with the following distributions:
  - Birth to 12 months: 5 RCTs<sup>12,18,25,30,33</sup>
  - >12 months to 18 months: 5 RCTs<sup>19,24,27,31,33</sup>
  - >18 to <2.5 years: 0 RCTs
  - 2.5 years to 7 years: 4 RCTs<sup>1,2,26,32,33</sup>

### ***Visual development***

- Six RCTs assessed visual development, including visual acuity (see **Table 5**). Of

those 6, 5 provided omega-3 fatty acid supplements during pregnancy alone,<sup>17,21,24,28,29</sup> and 1 during lactation alone.<sup>32,33</sup>

- The timing of visual development assessment in the children ranged from the neonatal period to 5 years postpartum, with the following distributions:
  - Birth to 6 months: 6 RCTs<sup>17,21,24,28,29,33</sup>
  - >6 months to 12 months: 2 RCTs<sup>24,33</sup>
  - >12 months to <5 years: 0 RCTs
  - 5 years: 1 RCTs<sup>32</sup>

### ***Social-emotional development***

- Eight RCTs assessed social-emotional development (**Table 6**). Of those 8, 7 provided omega-3 fatty acid supplements during pregnancy alone<sup>6,7,10-12,18,19,22,25-27</sup> and 1 during both pregnancy and lactation.<sup>1</sup>
- The timing of social-emotional development assessment in the children ranged from 1 week to 12 years postpartum, with the following distributions:
  - Birth to 12 months: 3 RCTs<sup>12,18,25</sup>
  - >12 months to 2 years: 2 RCTs<sup>19,27</sup>
  - >2 years to 5 years: 5 RCTs<sup>1,6,7,10,26</sup>
  - >5 years: 3 RCTs<sup>5,11,22</sup>

### ***Academic performance***

- One RCT assessed academic performance, including reading, spelling, and math computation at age 7 years among children of mothers who participated in an intervention during pregnancy alone (**Table 7**).<sup>11</sup>

### ***Anxiety and Depression***

- No studies meeting the inclusion criteria assessed anxiety or depression in children.

### ***ADD/ADHD***

- One RCT assessed hyperactivity disorders at 4 years<sup>10</sup> and ADHD at age 7 years<sup>11</sup> among children of mothers who participated in an intervention during pregnancy alone (**Table 7**).

### ***Autism spectrum disorder***

- Two studies assessed the risk of autism spectrum disorder in children (**Table 7**). One study was an RCT that supplemented mothers during pregnancy alone and assessed children at 4 years.<sup>10</sup> The other study was a PCS that assessed children at 36 months.<sup>16</sup>

## **Evidence synthesis**

The 33 articles from 16 studies, including 15 RCTs and 1 PCS, provided a substantial body of evidence to examine the relationship between omega-3 fatty acid supplementation during pregnancy and/or lactation and developmental milestones in the child. Among these studies, however, the time period of both the intervention/exposure and the outcome assessment varied widely. Furthermore, heterogeneity in the developmental domains assessed, as well as in the measures used to evaluate child performance in each of those domains, limited the ability to compare results across studies. Many of the assessment

tools administered in the included studies are widely used and have been validated for use in similar populations, including the Bayley Scales of Infant Development, the Wechsler scales of intelligence (WISC, WPPSI, and WASI), the Kaufman Assessment Battery for Children, and the Fagan Test of Infant Intelligence. However, the validity and reliability of any measure of neurobehavioral development depend on multiple factors, such as the appropriate administration of the assessment, the training of study personnel who administer the assessment, and the quality of data processing and statistical analysis; this detailed information was not provided in all studies. Further, whether an assessment is able to detect the effects of a nutrition intervention depends on its sensitivity to the functions, brain areas that are affected by the nutrient of interest and timing of assessment. This may be particularly relevant in populations without overt nutrient deficiencies, as the effects of interventions are smaller and thus require greater sensitivity of neurobehavioral assessments. Therefore, assessments targeting multiple cognitive functions, even within a single population may not produce consistent results.

Due to concerns about sample size, multiple testing without adjustment for multiple comparisons, and interpretability of interactions, only main effects were considered in this review. Key confounders were considered in this body of evidence. However, it was less of a concern because most of the studies included in this body of evidence were RCTs. Publication bias is always a consideration, however, it is not a serious concern for this body of evidence because 3 studies reported only non-significant findings<sup>1-4,16</sup> while the remaining studies report a mix of significant and non-significant results.

## **Cognitive development**

### ***Supplementation during pregnancy alone:***

#### *Summary:*

Five of 8 studies found a statistically significant, favorable effect of supplementation on at least one measure of child cognitive development (detailed in **Table 2**).<sup>5-7,10-12,19,26</sup> One study found a statistically significant, unfavorable effect of supplementation on a single measure of child cognitive development. Specifically, Makrides et al<sup>10</sup> and Gould et al<sup>11</sup> found that children of mothers who consumed omega-3 fatty acid supplements during pregnancy scored less favorably on a parent-reported measure of executive function at age 4 years and 7 years. All 8 RCTs also found no effect of treatment on at least one measure of cognitive development in children ages 1 week to 8.5 years.<sup>2-7,10-12,19,22-27,29</sup>

When examining the totality of the evidence a general pattern emerged of more favorable, as opposed to unfavorable, outcomes of cognitive development among children of women who consumed omega-3 fatty acid supplements during pregnancy. However, a number of measures across all studies showed no statistically significant treatment effect of omega-3 fatty acid supplementation on cognitive development in the child. No notable differences in the timing of the intervention/exposure, the dose or composition of omega-3 fatty acid supplements, nor in the timing or method of outcome assessment, could explain the mixed results.

## Assessment of the evidence<sup>v</sup>:

The following conclusion statement was based on 8 RCTs and was graded “limited.”

“**Limited** evidence suggests that omega-3 fatty acid supplementation during pregnancy may result in favorable **cognitive development** in the child.”

As outlined and described below, the body of evidence examining omega-3 fatty acid supplementation during pregnancy and cognitive development in the child was assessed for the following elements used when grading the strength of the evidence (see also **Table 8**).

- **Risk of bias** was graded as strong for the RCTs included in this body of evidence. Overall, the RCTs included in this body of evidence had strong designs, were well conducted, and had few major flaws, resulting in overall low risk of bias based on randomization, deviations from intended interventions, and outcome measurement for all studies. The few concerns noted were unlikely to alter the results, and are described below:
  - Two studies had probable differences in reasons for attrition between intervention and control groups, resulting in increased risk of bias due to missing outcome data.<sup>5,7,22</sup>
  - Generally, the included studies had some risk of bias due to selection of the reported results. Few studies published pre-registered analysis plans, and thus it was unclear whether the reported analyses were selected based on the outcome. However, given that the reported domains were generally consistent with pre-registered protocols and that all of the studies reported at least one non-statistically significant result, the risk was judged to be moderate.
  - One article reported analyses that were consistent with the published protocol,<sup>11</sup> but another study reported only some of the analyses outlined in the pre-published analysis plan.<sup>24</sup> Further, Catena et al<sup>4</sup> excluded children with >50 percent error on the Attention Network Task, but did not report the comparison of analyses with and without those data.
- **Consistency** was graded limited. Findings were mixed both within and between studies. These inconsistencies could not be explained by methodological differences, as there were no obvious differences in the specific timing or duration of the intervention, the composition or dose of the omega-3 fatty acid supplements or placebos, or in the timing or measurement tool for the outcome assessment that could explain the heterogeneity of the results. However, the wide variety in the timing of outcome assessments made it difficult to compare results across studies.
- **Directness** was graded as strong for the RCTs in this body of evidence. All studies were designed to examine an intervention of omega-3 fatty acid supplementation during pregnancy and with one exception,<sup>7,22</sup> the primary or pre-registered secondary outcome was cognitive development in the child.

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<sup>v</sup> A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews> and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

- **Precision** was graded as moderate for the studies. There were an adequate number of studies to investigate the relationship between omega-3 supplementation during pregnancy and cognitive development in children. Two studies had substantial sample sizes that, based on estimated effect sizes in similar studies, were likely sufficient to examine this relationship, especially at earlier outcome assessments.<sup>10,11,19,26,27</sup> Two studies reported power calculations suggesting that the studies were sufficiently powered.<sup>5,6,25</sup> Four studies generally did not report power calculations and it is unclear whether the final sample size was sufficiently powered.<sup>7,12,22-24</sup> In addition to power, number of studies that were included in the body of evidence and variability within and across studies were considered while grading precision. Overall, none of the studies unduly influenced the findings of this systematic review and removing a single study from this body of evidence would not likely change the conclusions.
- **Generalizability** was graded as moderate for this body of evidence. Two studies were conducted in the United States and both were from the same research group.<sup>5,6,12</sup> Minority women were generally underrepresented in this body of evidence. Two studies did not provide any information regarding race/ethnicity,<sup>2-4,10,11,19</sup> and 2 studies recruited primarily White participants.<sup>7,22-24</sup> However, the remaining 4 studies recruited primarily non-White participants, including the U.S.-based studies.<sup>5,6,12,25-27</sup> Regarding socioeconomic status, the studies mostly included women with post-secondary education. Participants were primarily adult women and none of the studies focused on adolescent mothers. For these reasons, the findings from this systematic review are somewhat applicable to the general U.S. population.

### ***Supplementation during pregnancy and lactation:***

#### *Summary:*

Three RCTs examined the effects of omega-3 fatty acid supplementation during both pregnancy and lactation on cognitive development in the child (ages 6 months to 7 years) (**Table 2**).<sup>1,13-15,31</sup> One study found a statistically significant, favorable effect of supplementation on one measure of intelligence in the child at age 4 years.<sup>15</sup> All 3 RCTs found no treatment effect on at least one measure of cognitive development from ages 6 months to 7 years.

#### *Assessment of the evidence:*

Given the mixed results and the small number of studies, risk of bias due to deviations from intended interventions because of large attrition rates (**Table 8**), and limited information on the generalizability of results to the general U.S. population, insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation and cognitive development in the child. Therefore, the body of evidence was rated 'grade not assignable.'

### ***Supplementation during lactation alone:***

#### *Summary:*

One RCT examined the effects of omega-3 fatty acid supplementation during lactation alone on cognitive development in the child (ages 2.5 years to 5 years) (**Table 2**).<sup>32,33</sup> Jensen et al<sup>32,33</sup> reported a statistically significant, favorable effect of supplementation on one measure of sustained attention in the child at age 5 years, as well as no association

with multiple measures of cognitive development at ages 12 months, 2.5 years, and 5 years.

*Assessment of the evidence:*

The entire body of evidence consisted of a single study with concerns regarding statistical power to detect effects in these secondary outcomes, risk of bias due to outcome measurement and deviations from the intended intervention (**Table 8**), and a sample that may not reflect the diversity of the general U.S. population. Therefore, insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during lactation alone and cognitive development in the child, and the body of evidence was rated 'grade not assignable.'

**Table 2. Description of evidence on relationship between omega-3 fatty acid supplementation and cognitive development<sup>vi</sup>**

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<b>Pregnancy only</b>				
<b>Campoy, 2011<sup>2</sup></b> <b>Germany, Hungary, Spain   NUHEAL</b> <b>N=154</b> Mothers were age ~31y and ~47% eligible for university entrance or degree. Race/ethnicity NR.	Placebo vs FO: 500mg/d DHA + 150 mg/d EPA vs 5-MTHF: 400 ug/d vs FO + 5-MTHF 20wk through delivery	Intelligence: K-ABC at 6.5y	Non-significant: All main effects • Mental Processing Composite • Sequential Processing Scale • Simultaneous Processing Scale	• Outcome assessor blinding NR, but standard methods used • Pre-registered analysis plan NR
<b>Catena, 2016<sup>4</sup></b> <b>Germany, Hungary, Spain   NUHEAL</b> <b>N=136</b> Mothers were age ~32y and ~43% eligible for university entrance or degree. Race/ethnicity NR.	Placebo vs FO: 500mg/d DHA + 150 mg/d EPA vs 5-MTHF: 400 ug/d vs FO + 5-MTHF 20wk through delivery	Attention/Executive function: Attention Network Task at 8.5y	Non-significant: All main effects • Total errors (%) • Interference errors (%) • Orienting errors (%) • Alerting errors (%)	• Excluded children with >50% conflict errors; comparison of results with and without those children NR • Pre-registered analysis plan NR

<sup>vi</sup> ABR: Auditory brainstem response; Adj: adjusted; ARA: arachidonic acid; ASQ: Ages and Stages Questionnaire; BRIEF: Behavior Rating Inventory of Executive Function-Preschool; BSID: Bayley Scales of Infant Development; CELF: Clinical Evaluation of Language Fundamentals; CI: confidence interval; DAS: Differential Ability Scales; DHA: docosahexaenoic acid; DOMInO: DHA to Optimize Mother Infant Outcome; EPA: eicosapentaenoic acid; FO: fish oil; FTII: Fagan Test of Infant Intelligence; GMDS: Griffiths Mental Development Scales; INFAT: The Impact of the Nutritional Fatty Acids During Pregnancy and Lactation for Early Human Adipose Tissue Development; IQ: intelligence quotient; ISI: interstimuli interval; K-ABC: Kaufman Assessment Battery for Children; K-CPT: Kiddie Continuous Performance Test; KUDOS: Kansas University DHA Outcomes Study; MSCA: McCarthy Scales of Children's Abilities; MTHF: methyl tetrahydrofolate; NBAS: Neonatal Behavioral Assessment Scale; NR: not reported; NUHEAL: Nutraceuticals for a Healthier Life; POSGRAD: Prenatal Omega 3 Supplementation on child Growth and Development; RAVLT: Rey Auditory Verbal Learning Test; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; RT: reaction time; TEACH: Test of Everyday Attention for Children; WASI: Wechsler Abbreviated Scale of Intelligence; WISC: Wechsler Intelligence Scale for Children; WMIC: working memory and inhibitory control; WPPSI: Wechsler Primary and Preschool Scale of Intelligence

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p><b>Catena, 2019<sup>3</sup></b>  <b>Spain   NUHEAL</b>  <b>N=74</b></p> <p>Mothers were age ~31y at delivery, 76% medium to high SES, and ~32% completed secondary education or higher. Race/Ethnicity: 100% White children.</p>	<p>Placebo vs  FO: 500mg/d DHA + 150 mg/d EPA vs  5-MTHF: 400 ug/d vs  FO + 5-MTHF  20wk through delivery</p>	<p>Intelligence: K-ABC-II  at 6.6y</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• Mental Processing Index</li> </ul>	<ul style="list-style-type: none"> <li>• Outcome assessor blinding NR, but standard methods used</li> <li>• Pre-registered analysis plan NR</li> </ul>
<p><b>Colombo, 2016<sup>5</sup></b>  <b>USA   KUDOS</b>  <b>N=156</b></p> <p>Mothers were age ~26y at enrollment, with mean income &lt;\$46K and ~14y education. Race/Ethnicity: 6% Hispanic, 31% Black.</p>	<p>600 mg/d DHA vs placebo (corn and soybean oils)  ~14.5wk through delivery</p>	<p>Visual learning: Visual habituation task with simultaneous heart rate  at 4mo, 6mo, 9mo</p>	<p><b>Significant:</b>  <b>Favors Intervention</b></p> <p>Attrition due to fussiness  Overall, P&lt;0.01  Control: N=64, Intervention: N=47</p> <p>at 6 mo, P&lt;0.001  Control: N=23, Intervention: N=6</p> <p>at 9 mo, P&lt;0.05  Control: N=22, Intervention: N=14</p> <p>Non-significant:  All other main effects</p> <ul style="list-style-type: none"> <li>• Peak look duration</li> <li>• Looks to habituation, P=0.056 <ul style="list-style-type: none"> <li>○ Faster habituation in DHA vs placebo</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Proportions and reasons for missingness differ, seemingly more dropout in placebo group</li> <li>• Major differences in those followed up and not followed up</li> <li>• Pre-registered data analysis plan NR</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p><b>Colombo, 2019<sup>6</sup></b>  <b>USA   KUDOS</b>  <b>N=161</b></p> <p>Mothers were age ~26y at enrollment, with mean income &lt;\$46K and ~14y education.  Race/Ethnicity: 6% Hispanic, 31% Black.</p>	<p>600 mg/d DHA vs placebo (corn and soybean oils)  ~14.5wk through delivery</p>	<p>BSID-II  at 18mo</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• Mental Development Index</li> <li>• Psychomotor Development Index</li> <li>• Behavior Rating Scale total</li> </ul>	<ul style="list-style-type: none"> <li>• (See Colombo, 2016)</li> <li>• More outcomes reported in the paper than on the clinical trials registry.</li> <li>• Pre-registered data analysis plan NR</li> </ul>
		<p>WPPSI-III  at 36, 48, 72mo</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• Verbal IQ</li> <li>• Performance IQ</li> <li>• Processing Speed</li> <li>• Full Scale IQ</li> </ul>	
		<p>Executive function: Willatts problem-solving task  at 10mo</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• Total score</li> </ul>	
		<p>Executive function: Delayed Response spatial memory task  at 24 and 30mo</p>	<p><b>Significant:</b>  <b>Favors intervention</b></p> <p>at 24 mo  Initial trials, P&lt;0.05  Effect size (d): 0.063</p> <p>Reversal trials, P&lt;0.05  Effect size (d): 0.278</p> <p>at 30 mo  Initial trials, P&lt;0.05  Effect size (d): 0.128</p>	

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
			Reversal trials, $P < 0.05$ Effect size (d): 0.340	
		Executive function: Dimensional Change Card Sort task and Stroop task at 36, 42, 48, 60mo	Non-significant: All main effects Dimensional Change Card <ul style="list-style-type: none"> <li>• Prestwich total</li> <li>• Postswitch total</li> <li>• Percent passing</li> </ul> Stroop task <ul style="list-style-type: none"> <li>• Total score</li> </ul>	
		Executive function: Tower of Hanoi at 60 and 72mo	Non-significant: All main effects <ul style="list-style-type: none"> <li>• Max steps</li> <li>• Efficiency</li> </ul>	
<b>Dunstan, 2008<sup>7</sup></b> <b>Australia</b> <b>N=72</b>  Mothers were age ~32y at enrollment and ~73% completed $\geq 12$ y education. Race/Ethnicity: 100% White.	2.2g/d DHA + 1.1 g/d EPA vs placebo (olive oil) 20wk through delivery	GMDS at 2.5y	<b>Significant:</b> <b>Favors Intervention</b> Eye and hand coordination subscale quotient $P = 0.021$ Control (Mean $\pm$ SD): 108.0 $\pm$ 11.3 Intervention: 114.0 $\pm$ 10.2  Non-significant: All other main effects <ul style="list-style-type: none"> <li>• Locomotor</li> <li>• Personal social</li> <li>• Speech and hearing</li> <li>• Performance</li> </ul>	<ul style="list-style-type: none"> <li>• Probable differences in reasons for attrition</li> <li>• No power calculation for neurobehavioral results</li> <li>• Pre-registered data analysis plan NR</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p><b>Gould, 2014<sup>10</sup></b>  <b>Australia   DOMInO</b>  <b>N=158</b></p> <p>Mothers were age ~30y at enrollment and ~65% completed secondary education.  Race/ethnicity NR.</p>	<p>800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo  18-21wk through delivery</p>	<p>Attention: Sustained attention (Single Object task) at 27 ± 2mo</p>	<ul style="list-style-type: none"> <li>• Practical reasoning</li> <li>• General quotient score</li> </ul> <p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• Total duration of time spent looking at the toy</li> <li>• Percentage of time spent looking at the toy</li> <li>• Average length of look at the toy</li> <li>• No. of looks at the toy</li> <li>• No. of times looked away from the toy</li> </ul>	<ul style="list-style-type: none"> <li>• Power calculation NR</li> <li>• Pre-registered analysis plan NR</li> </ul>
		<p>Attention: Sustained attention (Multiple Object task) at 27 ± 2mo</p>	<p><b>Significant:</b>  <b>Favors intervention</b></p> <p>No. of times looked away from toys  Adj P=0.03  Ref: Control  Mean Difference: -2.0, 95% CI: (-3.9, -0.2)</p> <p>Non-significant:  All other main effects</p> <ul style="list-style-type: none"> <li>• No. of times shifted looks between toys</li> <li>• Total duration of time looking at toys</li> <li>• Percentage of time spent looking at toys</li> </ul>	

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
		Attention: Distractibility (Multiple Object with distractor task) at 27 ± 2mo	<ul style="list-style-type: none"> <li>• Average length of a look at a toy</li> </ul> Non-significant: All main effects <ul style="list-style-type: none"> <li>• Average latency to turn to the distractor when attention was focused</li> <li>• Percentage of times distracted when focused</li> <li>• Average latency to look to the distractor when attention was casual</li> <li>• Percentage of times distracted when attention was casual</li> <li>• Total duration of time spent looking at the distractor when the distractor was on</li> <li>• Total duration of time spent looking at the distractor when the distractor was off</li> </ul>	
		WMIC: A-not-B task: at 27 ± 2mo	<b>Significant:</b> <b>Favors intervention</b> Average accuracy during training trials Adj P=0.05 Ref: Control Adj Mean Difference (mm): 14.4, 95% CI: (20.2, 29.1)  Non-significant: All other main effects <ul style="list-style-type: none"> <li>• Average accuracy during test trials</li> </ul>	

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p><b>Gould, 2017<sup>11</sup></b>  <b>Australia   DOMInO</b>  <b>N=543</b></p> <p>Mothers were age ~30y at enrollment and ~66% completed secondary education.  Race/ethnicity NR.</p>	<p>800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo  18-21wk through delivery</p>	<p>Executive function: TEACH Sky Search; RAVLT Trial 1 correct words; Rey Complex Figure Copy; Fruit Stroop Test; CELF-4  at 7y</p>	<p>Non-significant:  All main effects  TEACH Sky Search</p> <ul style="list-style-type: none"> <li>• Total</li> <li>• Score</li> <li>• Creature Counting</li> <li>• Sky Search Dual Task</li> </ul> <p>RAVLT</p> <ul style="list-style-type: none"> <li>• Trial 1 correct words</li> <li>• Total (trials 1-5) correct words</li> <li>• Delayed recall correct words</li> </ul> <p>Rey Complex Figure Copy</p> <ul style="list-style-type: none"> <li>• Raw score</li> <li>• Organizational raw score</li> </ul> <p>Fruit Stroop Test</p> <ul style="list-style-type: none"> <li>• Interference score</li> </ul> <p>CELF-4</p> <ul style="list-style-type: none"> <li>• Recall of digits total</li> </ul> <p><b>Significant:</b>  <b>Favors control</b>  Global executive composite  Adj P=0.01  Ref: Contol  Adj Mean Difference: 2.38, 95%  CI: (0.67, 4.08)</p>	<ul style="list-style-type: none"> <li>• No major limitations</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
			Behavioral regulation index Adj P=0.02 Ref: Contol Adj Mean Difference: 2.09, 95% CI: (0.40, 3.79)  Metacognitiion index Adj P=0.01 Ref: Contol Adj Mean Difference: 2.25, 95% CI: (0.57, 3.92)	
		Intelligence: WASI-II full scale IQ at 7y	<b>Significant:            Favors intervention</b> Perceptual reasoning Adj P=0.03 Ref: Control Adj Mean Difference: 2.01, 95% CI: (0.23, 3.79)  Non-significant: All other main effects <ul style="list-style-type: none"> <li>• Verbal comprehension</li> <li>• Full-scale IQ &lt;85</li> </ul>	
<b>Gustafson, 2013<sup>12</sup></b> <b>USA</b> <b>N=44</b>	600 mg/d DHA vs placebo (corn and soybean oils) 12-20wk through delivery	NBAS: Habituation, Orienting, Autonomic, and Reflexes scales at 1wk	<b>Significant:            Favors intervention</b> Autonomic, P=0.029 Control (Mean± SD): 14.83± 16.90	<ul style="list-style-type: none"> <li>• No power calculation</li> <li>• Pre-registered analysis plan NR</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p>Mothers were age ~26y at enrollment and completed ~14y education. Race/Ethnicity: 37.3% Black, 46.3% White, 13.4% Hispanic, 3% Asian.</p>			<p>Intervention: 18.13± 14.48</p> <p>Non-significant: All other main effects</p> <ul style="list-style-type: none"> <li>• Habituation</li> <li>• Orienting</li> <li>• Reflexes</li> </ul>	
<p><b>Makrides, 2010<sup>19</sup></b> <b>Australia   DOMInO</b> <b>N=694</b></p> <p>Mothers were age ~29y at enrollment and ~68% completed more than secondary education. Race/ethnicity NR.</p>	<p>800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo 18-21wk through delivery</p>	<p>BSID-III: Cognitive Scale, continuous, accelerated, and delayed at 18mo</p>	<p><b>Significant:</b> <b>Favors intervention</b></p> <p>Cognitive Standardized Score, Continuous &lt;85, Adj P=0.007 Ref: Control Adj RR: 0.41, 95% CI: (0.22, 0.78)</p> <p>Non-significant: All other main effects</p> <ul style="list-style-type: none"> <li>• Cognitive Standardized Score, Delayed</li> <li>• Cognitive Standardized Score, Accelerated</li> </ul>	<ul style="list-style-type: none"> <li>• Pre-registered analysis plan NR</li> </ul>
<p><b>Makrides, 2014<sup>20</sup></b> <b>Australia   DOMInO</b> <b>N=646</b></p> <p>Mothers were age ~29y at enrollment and ~68% completed more than secondary education. Race/ethnicity NR.</p>	<p>800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo 18-21wk through delivery</p>	<p>DAS-II: General Conceptual Ability, Non-verbal Reasoning, Verbal Reasoning, and Spatial Scales at 4y</p>	<p>Non-significant: All main effects</p> <ul style="list-style-type: none"> <li>• General Conceptual Ability Scale</li> <li>• Non-verbal Reasoning Scale</li> <li>• Verbal Reasoning Scale</li> <li>• Spatial Scale</li> </ul>	<ul style="list-style-type: none"> <li>• Pre-registered analysis plan NR</li> </ul>
		<p>Executive function: DAS II: Day-night Stroop</p>	<p>Non-significant:</p>	

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
		at 4y	All main effects DAS II <ul style="list-style-type: none"> <li>• Recall of Digits Forwards</li> <li>• Recognition of Pictures</li> </ul>	
		Parent-reported executive function: BRIEF at 4y	Day-night Stroop <hr/> <b>Significant:</b> Favors control Emergent Meta-Cognition Index Adj P=0.03 Ref: Contol Adj Mean Difference: 1.52, 95% CI: (0.11, 2.92)  Plan/Organize Scale Adj P=0.02 Ref: Contol Adj Mean Difference: 1.54, 95% CI: (0.21, 2.87)  Non-significant: All other main effects <ul style="list-style-type: none"> <li>• Global Executive Composite</li> <li>• Inhibitory Self-Control index</li> <li>• Flexibility Index</li> <li>• Inhibition Scale</li> <li>• Shift Scale</li> <li>• Emotional Control Scale</li> <li>• Working Memory Scale</li> </ul>	

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<b>Meldrum, 2015<sup>22</sup></b> <b>Australia</b> <b>N=48</b>  Mothers were age ~32y at enrollment and ~73% completed ≥12y education. Race/Ethnicity: 100% White.	2.2g/d DHA + 1.1 g/d EPA vs placebo (olive oil) 20wk through delivery	WISC-IV Beery-Buktenica Developmental Test of Visual-Motor Integration at 12y	Non-significant: All main effects WISC-IV <ul style="list-style-type: none"> <li>• Full Scale IQ</li> <li>• Verbal Comprehension</li> <li>• Perceptual Reasoning</li> <li>• Working Memory</li> <li>• Processing Speed</li> </ul> Beery-Buktenica <ul style="list-style-type: none"> <li>• Standard Score</li> <li>• Percentiles</li> </ul>	<ul style="list-style-type: none"> <li>• Among those followed to 12y, birth weight differed by treatment group</li> <li>• Possible differences in reasons for attrition</li> <li>• No power calculation, Likely under-powered</li> </ul>
<b>Mulder, 2013<sup>24</sup></b> <b>Canada</b> <b>N=154</b>  Mothers were age ~33y at enrollment and 94.4% completed post-secondary education. Race/Ethnicity: ~74% White.	400mg/d DHA vs placebo (corn and soybean oils) 16wk through delivery	Executive function: Willatts problem-solving task at 9mo   BSID-III at 18mo	Non-significant: All main effects <ul style="list-style-type: none"> <li>• Pass/fail</li> </ul>  Non-significant: All main effects (Risk that placebo group fails to achieve the outcome) <ul style="list-style-type: none"> <li>• Highest quartile cognitive score</li> </ul>	<ul style="list-style-type: none"> <li>• No power calculation</li> <li>• Pre-registered data analysis outlined multiple regression, not reported in the paper</li> </ul>
<b>Mulder, 2018<sup>23</sup></b> <b>Canada</b> <b>N=89</b>	400mg/d DHA vs placebo (corn and soybean oils) 16wk through delivery	K-ABC at 5.75y	Non-significant: All main effects <ul style="list-style-type: none"> <li>• Sequential Processing Scale</li> <li>• Learning Ability Scale</li> <li>• Simultaneous Processing Scale</li> <li>• Mental Performance Index</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear whether outcome assessors were blinded to treatment group</li> <li>• No power calculation</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
Mothers were age ~33y at enrollment and 94.4% completed post-secondary education. Race/Ethnicity: ~74% White.		Beery-Buktenica Developmental Test of Visual-Motor Integration at 5.75y	Non-significant: All main effects • Score	• Pre-registered analysis plan NR
		Test of Variables of Attention at 5.75y	Non-significant: All main effects • RT variability • RT • Errors of commission • Errors of omission	
<b>Ostadrhimi, 2018<sup>25</sup></b> <b>Iran</b> <b>N=146</b>  Mothers were age ~26y at enrollment and ~8% completed >12y education. ~19% had non-adequate family income. Race/ethnicity NR.	120mg/d DHA + 180mg/d EPA vs placebo (liquid paraffin) 16-20wk through delivery	Parent reported: ASQ-2 at 4mo and 6mo	Non-significant: All main effects Total • Subnormal development  Problem solving subscale • Mean score • Subnormal development	• Pre-registered analysis plan NR
<b>Ramakrishnan, 2015<sup>27</sup></b> <b>Mexico   POSGRAD</b> <b>N=730</b>  Mothers were age ~26y at enrollment and ~59% completed ≥12y education.	400mg/d DHA vs placebo (corn and soybean oils) 18-22wk through delivery	BSID-II: Mental Development Index at 18mo	Non-significant: All main effects • Mean score • Risk of delay	• Pre-registered data analysis NR
<b>Ramakrishnan, 2016<sup>26</sup></b> <b>Mexico   POSGRAD</b>	400mg/d DHA vs placebo (corn and soybean oils)	MSCA at 5y	Non-significant: All main effects	• Pre-registered data analysis NR

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p><b>N=797</b></p> <p>Mothers were age ~26y at enrollment and ~58% completed ≥12y education.</p>	18-22wk through delivery	<p>Attention: K-CPT at 5y</p>	<ul style="list-style-type: none"> <li>● Perceptual performance scale <ul style="list-style-type: none"> <li>○ Mean raw score</li> <li>○ Scale index score</li> </ul> </li> <li>● Quantitative scale <ul style="list-style-type: none"> <li>○ Mean raw score</li> <li>○ Scale index score</li> </ul> </li> <li>● Memory scale <ul style="list-style-type: none"> <li>○ Mean raw score</li> <li>○ Scale index score</li> </ul> </li> <li>● General cognitive scale <ul style="list-style-type: none"> <li>○ Mean raw score</li> <li>○ Scale index score</li> </ul> </li> </ul> <hr/> <p><b>Significant:</b></p> <p>Favors Intervention</p> <p>Inattention Corrected P&lt;0.0001</p> <p>T-score &lt;-1SD for omissions</p> <p>Control: 14.4%, Intervention: 25.7%</p> <p>T-score &gt;1SD for omissions</p> <p>Control: 16.2%, Intervention: 9.7%</p> <p>Non-significant:</p> <p>All other main effects</p> <p>Overall</p> <ul style="list-style-type: none"> <li>● Omissions score</li> <li>● Commissions <ul style="list-style-type: none"> <li>○ Score</li> <li>○ Score relative to standard sample</li> </ul> </li> <li>● Hit RT <ul style="list-style-type: none"> <li>○ Score</li> </ul> </li> </ul>	

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p><b>Stein, 2012<sup>29</sup></b>  <b>Mexico   POSGRAD</b>  <b>N=900</b></p> <p>Mothers were age ~26y at enrollment and ~58% completed ≥12y education.</p>	<p>400mg/d DHA vs placebo (corn and soybean oils)  18-22wk through delivery</p>	<p>ABR  at 1mo and 3mo</p>	<ul style="list-style-type: none"> <li>○ Score relative to standard sample</li> <li>● Response style score relative to standard sample</li> <li>● Overall score relative to standard sample</li> </ul> <p>Inattention scores</p> <ul style="list-style-type: none"> <li>● Hit RT, speed consistency</li> <li>● Variability</li> <li>● Detectability</li> <li>● Hit RT ISI change</li> <li>● Hit speed consistency ISI change</li> </ul> <p>Impulsivity scores</p> <ul style="list-style-type: none"> <li>● Perseverations</li> </ul> <p>Vigilance scores</p> <ul style="list-style-type: none"> <li>● Hit RT block change</li> <li>● Hit speed consistency by block change</li> </ul> <p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>● Latency 1</li> <li>● Latency 3</li> <li>● Latency 5</li> <li>● Interpeak latency 1-3</li> <li>● Interpeak latency 3-5</li> <li>● Interpeak latency 1-5</li> </ul>	<p>Pre-registered data analysis NR</p>
<p><b>Pregnancy and Lactation</b></p>				

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p><b>Brei, 2017<sup>1</sup></b>  <b>Germany   INFAT</b>  <b>N=130</b></p> <p>Mothers were age ~33y at enrollment and 73% completed ≥12y education. Race/Ethnicity: NR.</p>	<p>1020 mg/d DHA + 180 mg/d EPA + 9 mg/d Vitamin E vs general nutrition advice</p> <p>15wk gestation through 4mo postpartum</p>	<p>Parent reported: Child Development Inventory: General development, Numbers at 4y and 5y</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• General development scale classification (Normal, Borderline, Delay)</li> <li>• Numbers scale classification (Normal, Borderline, Delay)</li> </ul>	<ul style="list-style-type: none"> <li>• Reasons for missingness by group NR</li> <li>• Results were parent-reported</li> <li>• Pre-registered data analysis NR</li> </ul>
<p><b>Helland, 2001<sup>13</sup></b>  <b>Norway</b>  <b>N=245</b></p> <p>Mothers were age ~28y at enrollment and ~72% completed ≥12y education. Race/ethnicity: NR.</p>	<p>10mL/d cod liver oil vs placebo (corn oil)</p> <p>17-19wk gestation through 3mo postpartum</p>	<p>Memory: FTII at 6mo and 9mo</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• Novelty preference <ul style="list-style-type: none"> <li>○ 6mo only</li> <li>○ 9mo only</li> <li>○ 6mo and 9mo combined</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Details of allocation sequence NR</li> <li>• 38% withdrew before delivery, many due to non-adherence or "discomfort taking the oil"</li> <li>• Nearly 60% attrition, unclear if reasons for missingness were balanced across groups</li> <li>• N=130 infants received cod liver oil, per Norwegian recs but NR by groups</li> <li>• No evidence of performance above chance in either group</li> <li>• Pre-registered analysis NR</li> </ul>
<p><b>Helland, 2003<sup>15</sup></b>  <b>Norway</b></p>	<p>10mL/d cod liver oil vs placebo (corn oil)</p>	<p>Intelligence: K-ABC at 4y</p>	<p><b>Significant:  Favors Intervention</b></p>	<ul style="list-style-type: none"> <li>• Substantial attrition, unclear if reasons for missingness</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p><b>N=84</b></p> <p>Mothers were age ~28y at enrollment and ~73% completed ≥12y education. Race/ethnicity: NR.</p>	17-19wk gestation through 3mo postpartum		<p>Mental Processing Composite, P=0.049</p> <p>Control (Mean± SD): 102.3± 11.3</p> <p>Intervention: 106.4± 7.4</p> <p>Non-significant:</p> <p>All other main effects</p> <ul style="list-style-type: none"> <li>• Sequential Processing scale</li> <li>• Simultaneous Processing scale</li> <li>• Nonverbal scale</li> </ul>	were balanced across groups
<p><b>Helland, 2008<sup>14</sup></b></p> <p><b>Norway</b></p> <p><b>N=143</b></p> <p>Mothers were age ~29y at delivery, with mean education 14.9y. Race/ethnicity: NR.</p>	<p>10mL/d cod liver oil vs placebo (corn oil)</p> <p>17-19wk gestation through 3mo postpartum</p>	Intelligence: K-ABC at 7y	<p>Non-significant:</p> <p>All main effects</p> <ul style="list-style-type: none"> <li>• Mental Processing Composite</li> <li>• Sequential Processing scale</li> <li>• Simultaneous Processing scale</li> <li>• Nonverbal scale</li> </ul>	<ul style="list-style-type: none"> <li>• See Helland, 2001 and Helland, 2003</li> </ul>
<p><b>van Goor, 2011<sup>31</sup></b></p> <p><b>The Netherlands</b></p> <p><b>N=114</b></p> <p>Mothers were age ~33y at enrollment and ~75% completed ≥12y education. Race/ethnicity: NR.</p>	<p>220mg/d DHA + 220mg/d ARA vs 220mg/d DHA + placebo (soy) vs 2 placebos (soy)</p> <p>14-20wk gestation through 3mo postpartum</p>	BSID-II (Dutch edition) at 18mo	<p>Non-significant:</p> <p>All main effects</p> <ul style="list-style-type: none"> <li>• Mental developmental scale</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear power to find results, but attrition and reasons reasonably balanced</li> <li>• Unclear whether outcomes would be affected by unblinded assessors</li> </ul>
<b>Lactation only</b>				
<p><b>Jensen, 2005<sup>33</sup></b></p> <p><b>USA</b></p> <p><b>N=160</b></p>	200mg/d DHA vs placebo (corn and soybean oils) 5d through 4mo postpartum	BSID-II: Mental development scale at 2.5y	<p>Non-significant:</p> <p>All main effects</p> <ul style="list-style-type: none"> <li>• Mean score</li> </ul>	<ul style="list-style-type: none"> <li>• Statistical power estimate based on other outcomes</li> <li>• Pre-registered data analysis NR</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
Mothers were age ~32y at enrollment, with mean education 16y. Race/ethnicity of children: 77% White, ~16% Black, ~6% Hispanic.		Visual-motor problem-solving: Clinical Adaptive Test at 12mo and 2.5y	Non-significant: All main effects • Mean score	
<b>Jensen, 2010<sup>32</sup></b> <b>USA</b> <b>N=118</b>	200mg/d DHA vs placebo (corn and soybean oils) 5d through 4mo postpartum	WPPSI-R at 5y	Non-significant: All main effects • Information Subset score • Block Design Subtest score	• Statistical power estimate based on other outcomes • Pre-registered data analysis NR
Mothers were age ~32y at enrollment, with mean education 16y. Race/ethnicity of children: 79% White, ~14% Black, ~6% Hispanic.		Executive function: WPPSI-R; K-ABC at 5y	Non-significant: All main effects WPPSI-R • Animal Pegs Subset score  K-ABC • Hand Movement Subscale score	
		Visual-motor integration: Developmental Test of Visual-Motor Integration-III at 5y	Non-significant: All main effects • Visual component score • Motor component score	

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
		Sustained attention: Leiter International Performance Scale-Revised: at 5y	<b>Significant:</b> <b>Favors intervention</b> Sustained attention subtest, P=0.008 Control (Mean± SD): 41.8± 9.3 Intervention: 46.5± 8.9	

## Language development

### **Supplementation during pregnancy alone:**

#### *Summary:*

Seven RCTs examined the effects of omega-3 fatty acid supplementation during pregnancy alone on language development in the child (**Table 3**).<sup>6,7,10,11,18,19,22-26</sup> All 7 RCTs, which assessed children from ages 3 months to 12 years, found no effect of treatment on at least one measure of language development.

Two studies found statistically significant, favorable effects of supplementation on at least one measure of language development in the child at ages 4 months,<sup>25</sup> and ages 14 and 18 months.<sup>24</sup> Notably, Ostadrahimi et al<sup>25</sup> found a benefit on a continuous measure of language at 4 months, but no effect on this continuous measure at 6 months, nor on the risk of subnormal language development at either age.

#### *Assessment of the evidence<sup>vii</sup>:*

Given the mixed results and some concerns regarding risk of bias due to selection of reported results (**Table 8**), insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during pregnancy alone and language development in the child, and therefore the body of evidence was rated ‘grade not assignable.’

### **Supplementation during both pregnancy and lactation:**

#### *Summary:*

One RCT examined the effects of omega-3 fatty acid supplementation during both pregnancy and lactation on language development in the child,<sup>1</sup> and reported a statistically significant favorable effect for a single measure of language development at age 5 years, but no association with other measures from the same tool at ages 4 years and 5 years (**Table 3**).

#### *Assessment of the evidence:*

The entire body of evidence consisted of a single study, with concerns regarding statistical power to detect effects in these secondary outcomes, and limited information on the generalizability of results to the general U.S. population. Therefore, insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation and language development in the child, and the body of evidence was rated ‘grade not assignable.’

### **Supplementation during lactation alone:**

#### *Summary:*

One RCT examined the effects of omega-3 fatty acid supplementation during lactation alone on language development in the child (**Table 3**).<sup>32,33</sup> Jensen et al<sup>32,33</sup> reported no

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<sup>vii</sup> A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews> and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

association with multiple measures of language development at ages 12 months, 2.5 years, and 5 years.

*Assessment of the evidence:*

The entire body of evidence consisted of a single study with concerns regarding statistical power to detect effects in these secondary outcomes, risk of bias due to outcome measurement and deviations from the intended intervention (**Table 8**), and a sample that may not reflect the diversity of the general U.S. population. Therefore, insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during lactation alone and language development in the child, and the body of evidence was rated 'grade not assignable.'

**Table 3. Description of evidence on relationship between omega-3 fatty acid supplementation and language development<sup>viii</sup>**

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<b>Pregnancy only</b>				
<b>Colombo, 2019<sup>6</sup></b> <b>USA   KUDOS</b> <b>N=161</b>  Mothers were age ~26y at enrollment, with mean income <\$46K and ~14y education. Race/Ethnicity: 6% Hispanic, 31% Black.	600 mg/d DHA vs placebo (corn and soybean oils) ~14.5wk through delivery	MacArthur-Bates CDI at 18mo	Non-significant: All main effects • Words Produced • Sentence Length • Complexity	• More outcomes reported in the paper than on the clinical trials registry • Pre-registered data analysis plan NR
		TOPEL at 42mo	Non-significant: All main effects • Early Literacy Index	
		Sentence Repetition tasks at 36, 42, 48mo	Non-significant: All main effects • Score	
		PPVT, Third Edition at 5y	Non-significant: All main effects • Standard Score	
<b>Dunstan, 2008<sup>7</sup></b> <b>Australia</b>	2.2g/d DHA + 1.1 g/d EPA vs placebo (olive oil) 20wk through delivery	Language Development Survey; Receptive: PPVT-III A	Non-significant: All main effects	• Probable differences in reasons for attrition

<sup>viii</sup> Adj: adjusted; ASQ: Ages and Stages Questionnaire; BSID: Bayley Scales of Infant Development; CDI: Communicative Development Inventory; CELF(-P2): Clinical Evaluation of Language Fundamentals (Preschool, second edition); CI: confidence interval; CLAMS: Clinical Linguistic and Auditory Milestone Scale; DHA: docosahexaenoic acid; DOMInO: DHA to Optimize Mother Infant Outcome; EPA: eicosapentaenoic acid; ETA: eicosatetraenoic acid; INFAT: The Impact of the Nutritional Fatty Acids During Pregnancy and Lactation for Early Human Adipose Tissue Development; KUDOS: Kansas University DHA Outcomes Study; MSCA: McCarthy Scales of Children's Abilities; NR: not reported; PPVT: Peabody Picture Vocabulary Test; RCT: randomized controlled trial; TOPEL: Test of Preschool Early Literacy; WPPSI-R: Wechsler Primary and Preschool Scale of Intelligence-Revised

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p><b>N=72</b></p> <p>Mothers were age ~32y at enrollment and ~73% completed ≥12y education. Race/Ethnicity: 100% White.</p>		at 2.5y	<ul style="list-style-type: none"> <li>Standard Score</li> </ul>	<ul style="list-style-type: none"> <li>No power calculation for neurobehavioral results</li> <li>Pre-registered data analysis plan NR</li> </ul>
<p><b>Gould, 2017<sup>11</sup></b> <b>Australia   DOMInO</b> <b>N=543</b></p> <p>Mothers were age ~30y at enrollment and ~66% completed secondary education. Race/ethnicity NR.</p>	<p>800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo 18-21wk through delivery</p>	<p>CELF-4: Core language score at 7y</p>	<p>Non-significant: All main effects</p> <ul style="list-style-type: none"> <li>Score</li> </ul>	<ul style="list-style-type: none"> <li>No major limitations</li> </ul>
<p><b>Keenan, 2016<sup>18</sup></b> <b>USA</b> <b>N=49</b></p> <p>Age 20-30y. 100% Medicaid eligible. Race/Ethnicity: 100% Black.</p>	<p>450 mg/d DHA + 40 mg/d DPA + 40 mg/d ETA + 90 mg/d EPA + 10 mg/d Vitamin E vs 990 mg/d soybean oil + 16.5 mg/d Vitamin E + 10 mg/d EPA + 10 mg/d DHA 16-21wk for 6wk</p>	<p>BSID-III: Receptive and Expressive Communication at 3mo</p>	<p>Non-significant: All main effects</p> <ul style="list-style-type: none"> <li>Receptive Communication</li> <li>Expressive Communication</li> </ul>	<ul style="list-style-type: none"> <li>Reasons for missingness by group NR</li> <li>Pre-registered data analysis plan NR</li> </ul>
<p><b>Makrides, 2010<sup>19</sup></b> <b>Australia   DOMInO</b> <b>N=694</b></p> <p>Mothers were age ~29y at enrollment and ~68% completed more than secondary education. Race/ethnicity NR.</p>	<p>800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo 18-21wk through delivery</p>	<p>BSID-III: Language Scale, continuous, delayed, and accelerated at 18mo</p>	<p>Non-significant: All main effects</p> <ul style="list-style-type: none"> <li>Language Standardized Score, Continuous</li> <li>Language Standardized Score, Delayed</li> <li>Language Standardized Score, Accelerated</li> </ul>	<ul style="list-style-type: none"> <li>Pre-registered analysis plan NR</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p><b>Makrides, 2014<sup>20</sup></b>  <b>Australia   DOMInO</b>  <b>N=646</b></p> <p>Mothers were age ~29y at enrollment and ~68% completed more than secondary education. Race/ethnicity NR.</p>	<p>800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo  18-21wk through delivery</p>	<p>CELF-P2  at 4y</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• Core language score</li> </ul>	<ul style="list-style-type: none"> <li>• Pre-registered analysis plan NR</li> </ul>
<p><b>Meldrum, 2015</b>  <b>Australia</b>  <b>N=48</b></p> <p>Mothers were age ~32y at enrollment and ~73% completed ≥12y education. Race/Ethnicity: 100% White.</p>	<p>2.2g/d DHA + 1.1 g/d EPA vs placebo (olive oil)  20wk through delivery</p>	<p>Child Communication Checklist  at 12y</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• Percentile rank</li> </ul>	<ul style="list-style-type: none"> <li>• Among those followed to 12y, birth weight differed by treatment group</li> <li>• Possible differences in reasons for attrition</li> <li>• No power calculation, Likely under-powered</li> </ul>
<p><b>Mulder, 2013<sup>24</sup></b>  <b>Canada</b>  <b>N=154</b></p> <p>Mothers were age ~33y at enrollment and 94.4% completed post-secondary education. Race/Ethnicity: ~74% White.</p>	<p>400mg/d DHA vs placebo (corn and soybean oils)  16wk through delivery</p>	<p>Non-native consonant recognition task  at 9mo</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• Pass/Fail</li> </ul>	<ul style="list-style-type: none"> <li>• No power calculation</li> <li>• Pre-registered data analysis outlined multiple regression, NR in paper</li> </ul>
		<p>MacArthur Infant CDI  at 14mo</p>	<p><b>Significant:</b>  <b>Favors intervention</b></p> <p>All main effects (Risk that placebo group fails to achieve the outcome)  Highest quartile words understood</p>	

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
			Adj P=0.002 Adj OR: 3.22, 95% CI: (1.49-6.94)	
			Highest quartile words produced Adj P=0.009 Adj OR: 2.61, 95% CI: (1.22-5.58)	
		MacArthur Infant and Toddler CDI at 18mo	<b>Significant:            Favors intervention</b> All other main effects (Risk that placebo group fails to achieve the outcome) Infant Highest quartile words understood Adj P=0.01 Adj OR: 2.77, 95% CI: (1.23-6.28)  Toddler Highest quartile words produced Adj P=0.02 Adj OR: 2.60, 95% CI: (1.15-5.89)	
			Non-significant: Infant Highest quartile words produced	
		BSID-III: Language composite scale	<b>Significant:            Favors intervention</b>	

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
		at 18mo	(Risk that placebo group fails to achieve the outcome) Receptive language Adj P=0.03 Adj OR: 2.23, 95% CI: (1.08, 4.60)  Non-significant: Expressive language	
<b>Mulder, 2018<sup>23</sup></b> <b>Canada</b> <b>N=89</b>  Mothers were age ~33y at enrollment and 94.4% completed post-secondary education. Race/Ethnicity: ~74% White.	400mg/d DHA vs placebo (corn and soybean oils) 16wk through delivery	Receptive: PPVT-4 at 5.75y	Non-significant: All main effects • Score	<ul style="list-style-type: none"> <li>• Unclear whether outcome assessors were blinded to treatment group</li> <li>• No power calculation</li> <li>• Pre-registered analysis plan NR</li> </ul>
<b>Ostadrhimi, 2018<sup>25</sup></b> <b>Iran</b> <b>N=146</b>  Mothers were age ~26y at enrollment and ~8% completed >12y education. ~19% had non-adequate family income. Race/ethnicity NR.	120mg/d DHA + 180mg/d EPA vs placebo (liquid paraffin) 16-20wk through delivery	Parent reported: ASQ-2 Communication subscale at 4mo	<p><b>Significant:</b> <b>Favors intervention</b> 4mo, mean score Adj P=0.02 Ref: Control Adj Mean Difference: 2.63, 95% CI: (0.36, 4.89)</p> <p>Non-significant: All other main effects • Mean score • Subnormal development</p>	<ul style="list-style-type: none"> <li>• Pre-registered analysis plan NR</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
		Communication subscale at 6mo	Non-significant: All other main effects • Mean score • Subnormal development	
<b>Ramakrishnan, 2016</b> <sup>26</sup> <b>Mexico</b> <b>N=797</b>  Mothers were age ~26y at enrollment and ~58% completed ≥12y education.	400mg/d DHA vs placebo (corn and soybean oils) 18-22wk through delivery	MSCA: Verbal scale at 5y	Non-significant: All main effects • Mean raw score • Mean scale index score	• Pre-registered data analysis NR
<b>Pregnancy and Lactation</b>				
<b>Brei, 2017</b> <sup>1</sup> <b>Germany   INFAT</b> <b>N=130</b>  Mothers were age ~33y at enrollment and 73% completed ≥12y education. Race/Ethnicity: NR.	1020 mg/d DHA + 180 mg/d EPA + 9 mg/d Vitamin E vs general nutrition advice 15wk gestation through 4mo postpartum	Parent reported: Child Development Inventory: Expressive, language comprehension, letters scales at 4y and 5y	<b>Significant:</b> Favors intervention Letter scales at 5y Borderline/developmentally delayed, P=0.043 Control: N=4 of 60 Intervention: N=0 of 70  <b>Non-significant:</b> All other main effects • Expressive language scale classification (Normal, Borderline, Delay) • Language comprehension scale classification (Normal, Borderline, Delay)	• Reasons for missingness by group NR • Results were parent-reported • Pre-registered data analysis NR
<b>Lactation only</b>				

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p><b>Jensen, 2005<sup>33</sup></b>  <b>USA</b>  <b>N=160</b></p> <p>Mothers were age ~32y at enrollment, with mean education 16y. Race/ethnicity of children: 77% White, ~16% Black, ~6% Hispanic.</p>	<p>200mg/d DHA vs placebo (corn and soybean oils)  5d through 4mo postpartum</p>	<p>CLAMS  at 12mo and 2.5y</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• Mean score</li> </ul>	<ul style="list-style-type: none"> <li>• Statistical power estimate based on other outcomes</li> <li>• Pre-registered data analysis NR</li> </ul>
<p><b>Jensen, 2010<sup>32</sup></b>  <b>USA</b>  <b>N=118</b></p> <p>Mothers were age ~32y at enrollment, with mean education 16y. Race/ethnicity of children: 79% White, ~14% Black, ~6% Hispanic.</p>	<p>200mg/d DHA vs placebo (corn and soybean oils)  5d through 4mo postpartum</p>	<p>WPPSI-R  at 5y</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• Vocabulary Subtest score</li> </ul>	<ul style="list-style-type: none"> <li>• Statistical power estimate based on other outcomes</li> <li>• Pre-registered data analysis NR</li> </ul>

## **Motor development**

### ***Supplementation during pregnancy alone:***

#### *Summary:*

Seven RCTs examined the effects of omega-3 fatty acid supplementation during pregnancy alone on motor development in the child (ages 1 week to 5.5 years)<sup>2,12,18,19,24-27</sup> (**Table 4**). Of those 7 RCTs, 6 found no treatment effect on at least one measure of motor development among children ages 1 week to 5.5 years.<sup>2,18,19,24-27</sup> Gustafson et al<sup>12</sup> found statistically significant, favorable effects of supplementation on a single measure of motor function in the neonate.

#### *Assessment of the evidence<sup>ix</sup>:*

Given the mixed results and concerns regarding risk of bias due to missing outcome data, outcome measurement, and selection of reported results, insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during pregnancy alone and motor development in the child, and therefore the body of evidence was rated 'grade not assignable.'

### ***Supplementation during both pregnancy and lactation:***

#### *Summary:*

Both of the RCTs that examined the effect of omega-3 fatty acid supplementation during both pregnancy and lactation found no statistically significant effect on at least one measure of motor development in the child (ages 2 weeks to 5 years)<sup>1,30,31</sup> (**Table 4**). Brei et al<sup>1</sup> found that a single measure of motor development, namely, the mirror movement ratio in the dominant hand only at 5 years, was more favorable in the intervention group than in the control group, but no other measures were statistically significantly different. At 2 weeks and 12 weeks postpartum, van Goor et al<sup>30</sup> found that infants whose mothers consumed DHA had a greater risk of mildly abnormal general movements compared to infants whose mothers consumed placebo. There were no differences in quality of general movements among infants whose mothers consumed DHA+ARA versus placebo or whose mothers consumed DHA+ARA versus DHA. Notably, the rates of mildly abnormal movements exceeded rates in other studies of healthy infants, and thus the authors disclosed blinding and discontinued the intervention before reaching recruitment goals.

#### *Assessment of the evidence:*

Given the mixed results, the early discontinuation of one of the trials (due to adverse effects of DHA supplements), concerns regarding risk of bias due to outcome measurement and selection of reported results, and limited information on the generalizability of results to the general U.S. population, insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation and motor development in the child, and therefore the body of evidence was rated 'grade not assignable.'

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<sup>ix</sup> A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews> and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

### ***Supplementation during lactation alone:***

#### *Summary:*

A single RCT examined the effect of omega-3 fatty acid supplementation during lactation alone on motor development in the child (ages 12 months to 5 years)<sup>32,33</sup> (**Table 4**). Jensen et al<sup>32,33</sup> reported higher scores on one measure of motor development at age ~2.5 years,<sup>33</sup> and the authors noted that scores in both the supplemented and placebo groups were higher than in other studies of healthy toddlers. Additional results revealed no association with other measures of motor development at ages 12 months, 2.5 years, and 5 years.

#### *Assessment of the evidence:*

The entire body of evidence consisted of a single study with concerns regarding statistical power to detect effects in these secondary outcomes, risk of bias due to outcome measurement and deviations from the intended intervention (**Table 8**), and a sample that may not reflect the diversity of the general U.S. population. Therefore, insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during lactation alone and motor development in the child, and the body of evidence was rated 'grade not assignable.'

**Table 4. Description of evidence on relationship between omega-3 fatty acid supplementation and motor development<sup>x</sup>**

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<b>Pregnancy Only</b>				
<b>Escolano-Margarit, 2011<sup>8</sup></b> <b>Germany, Hungary, Spain   NUHEAL</b> <b>N=167</b>  Mothers were age ~31y at enrollment and ~48% eligible for university entrance or degree. Race/ethnicity NR.	Placebo vs FO: 500mg/d DHA + 150 mg/d EPA vs 5-MTHF: 400 ug/d vs FO + 5-MTHF  20wk through delivery	Hempel Assessment at 4y	Non-significant: All main effects • Clinical conclusion (normal, simple MND, complex MND) • NOS • Fluency score	• Outcome assessor binding NR, but standard methods used • Pre-registered analysis plan NR
		Touwen Assessment at 5.5y	Non-significant: All main effects • Clinical conclusion (normal, simple MND, complex MND) • NOS	
<b>Gustafson, 2013<sup>12</sup></b> <b>USA</b> <b>N=44</b>  Mothers were age ~26y at enrollment and completed ~14y education. Race/Ethnicity:	600 mg/d DHA vs placebo (corn and soybean oils)  12-20wk through delivery	NBAS Motor scale at 1wk	<b>Significant:</b> <b>Favors intervention</b> Adj P=0.038  Control (Mean± SD): 23.08± 11.40  Intervention: 26.07± 18.13	• No power calculation • Pre-registered analysis plan NR

<sup>x</sup> Adj: adjusted; ARA: arachidonic acid; ASQ: Ages and Stages Questionnaire; BSID: Bayley Scales of Infant Development; CI: confidence interval; DHA: docosahexaenoic acid; DOMInO: DHA to Optimize Mother Infant Outcome; EPA: eicosapentaenoic acid; ETA: eicosatetraenoic acid; FO: fish oil; K-ABC: Kaufman Assessment Battery for Children; MSCA: McCarthy Scales of Children's Abilities; MND: minor neurological dysfunction; MTHF: methyl tetrahydrofolate; NOS: neurological optimality score; NR: not reported; NUHEAL: Nutraceuticals for a Healthier Life; POSGRAD: Prenatal Omega 3 Supplementation on child Growth and Development; RCT: randomized controlled trial

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
37.3% Black, 46.3% White, 13.4% Hispanic, 3% Asian.				
<b>Keenan, 2016<sup>18</sup></b> <b>USA</b> <b>N=49</b>  Age 20-30y. 100% Medicaid eligible. Race/Ethnicity: 100% Black.	450 mg/d DHA + 40 mg/d DPA + 40 mg/d ETA + 90 mg/d EPA + 10 mg/d Vitamin E  990 mg/d soybean oil + 16.5 mg/d Vitamin E + 10 mg/d EPA + 10 mg/d DHA  16-21wk for 6wk	BSID-III: Fine motor and gross motor scales  at 3mo	Non-significant: All main effects <ul style="list-style-type: none"> <li>• Fine motor scale</li> <li>• Gross motor scale</li> </ul>	<ul style="list-style-type: none"> <li>• Reasons for missingness by group NR</li> <li>• Pre-registered data analysis plan NR</li> </ul>
<b>Makrides, 2010<sup>19</sup></b> <b>Australia   DOMInO</b> <b>N=694</b>  Mothers were age ~29y at enrollment and ~68% completed more than secondary education. Race/ethnicity NR.	800mg/d DHA + 100 mg/d EPA vs Vegetable oil placebo  18-21wk through delivery	BSID-III: Motor subscale  at 18mo	Non-significant: All main effects  Motor Standardized Score	<ul style="list-style-type: none"> <li>• Pre-registered analysis plan NR</li> </ul>
<b>Mulder, 2013<sup>24</sup></b> <b>Canada</b> <b>N=154</b>  Mothers were age ~33y at enrollment and 94.4% completed post-secondary education. Race/Ethnicity: ~74% White.	400mg/d DHA vs placebo (corn and soybean oils)  16wk through delivery	BSID-III: Fine motor and gross motor scales  at 18mo	Non-significant: All main effects (Risk the placebo group fails to achieve the outcome)  <ul style="list-style-type: none"> <li>• Highest quartile fine motor score</li> <li>• Highest quartile gross motor score</li> </ul>	<ul style="list-style-type: none"> <li>• No power calculation</li> <li>• Pre-registered data analysis outlined multiple regression, NR in paper</li> </ul>
<b>Ostadrahimi, 2018<sup>25</sup></b> <b>Iran</b> <b>N=146</b>	120mg/d DHA + 180mg/d EPA vs placebo (liquid paraffin)  16-20wk through delivery	Parent reported: ASQ-2 Fine and Gross motor subscales  at 4mo and 6mo	Non-significant: All main effects  <ul style="list-style-type: none"> <li>• Mean scores</li> <li>• Subnormal development</li> </ul>	<ul style="list-style-type: none"> <li>• Pre-registered analysis plan NR</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p>Mothers were age ~26y at enrollment and ~8% completed &gt;12y education. ~19% had non-adequate family income. Race/ethnicity NR.</p>				
<p><b>Ramakrishnan, 2015<sup>27</sup></b> <b>Mexico   POSGRAD</b> <b>N=730</b></p>	<p>400mg/d DHA vs placebo (corn and soybean oils) 18-22wk through delivery</p>	<p>BSID-II: Psychomotor Scale at 18mo</p>	<p>Non-significant: All main effects</p> <ul style="list-style-type: none"> <li>• Mean score</li> <li>• Risk of delay</li> </ul>	<ul style="list-style-type: none"> <li>• Pre-registered data analysis NR</li> </ul>
<p>Mothers were age ~26y at enrollment and ~59% completed ≥12y education.</p>				
<p><b>Ramakrishnan, 2016<sup>26</sup></b> <b>Mexico   POSGRAD</b> <b>N=797</b></p>	<p>400mg/d DHA vs placebo (corn and soybean oils) 18-22wk through delivery</p>	<p>MSCA: Motor score at 5y</p>	<p>Non-significant: All main effects</p> <ul style="list-style-type: none"> <li>• Mean raw score</li> <li>• Mean scale index score</li> </ul>	<ul style="list-style-type: none"> <li>• Pre-registered data analysis NR</li> </ul>
<p>Mothers were age ~26y at enrollment and ~58% completed ≥12y education.</p>				
<b>Pregnancy and Lactation</b>				
<p><b>van Goor, 2010<sup>30</sup></b> <b>The Netherlands</b> <b>N=119</b></p>	<p>220mg/d DHA + 220mg/d ARA vs 220mg/d DHA + placebo (soy) vs 2 placebos (soy) 14-20wk through 3mo postpartum</p>	<p>Neonatal neurological classification at 2wk</p>	<p>Non-significant: All main effects</p> <ul style="list-style-type: none"> <li>• Mildly abnormal</li> </ul>	<ul style="list-style-type: none"> <li>• &gt;30% attrition before delivery</li> <li>• Early trial discontinuation due to high incidence mildly abnormal general movements at 12wk in DHA group</li> <li>• Participant &amp; assessors unblinded at trial discontinuation</li> <li>• Pre-registered data analysis NR</li> </ul>
<p>Mothers were age ~33y at enrollment and ~71% completed ≥12y education. Race/ethnicity: NR.</p>				

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
		General movements at 2wk	<b>Significant:</b> <b>Favors control</b> Mildly abnormal Control vs DHA Adj P=0.021 Adj $\beta$ : 3.867, 95% CI: (1.228, 12.173)	
		General movements at 12wk	<b>Significant:</b> <b>Favors control</b> Mildly abnormal Control vs DHA Adj P=0.014 Adj $\beta$ : 4.121, 95% CI: (1.335, 12.719)	
		Neurological optimality score (NOS) at 12wk	Non-significant: All main effects • Score	
<b>van Goor, 2011<sup>31</sup></b> <b>The Netherlands</b> <b>N=114</b>  Mothers were age ~33y at enrollment and ~75% completed $\geq$ 12y education. Race/ethnicity: NR.	220mg/d DHA + 220mg/d ARA vs 220mg/d DHA + placebo (soy) vs 2 placebos (soy) 14-20wk through 3mo postpartum	Hempel Assessment at 18mo	Non-significant: All main effects • Neurological optimality score • Fluency score • Normal neurological condition • Simple MND • Complex MND	• Unclear power to find results, but attrition and reasons reasonably balanced • Unclear whether outcomes would be affected by unblinded assessors
		BSID-II (Dutch edition) at 18mo	Non-significant: All main effects • Psychomotor developmental index	• BSID not mentioned in protocol



Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
77% White, ~16% Black, ~6% Hispanic.		Gesell Developmental Inventory at 12mo and 2.5y	Non-significant: All main effects • Mean score	
<b>Jensen, 2010<sup>32</sup></b> <b>USA</b> <b>N=118</b>  Mothers were age ~32y at enrollment, with mean education 16y. Race/ethnicity of children: 79% White, ~14% Black, ~6% Hispanic.	200mg/d DHA vs placebo (corn and soybean oils) 5d through 4mo postpartum	Gross motor: MSCA; K-ABC at 5y	Non-significant: All main effects MSCA • Leg Coordination subscale score  K-ABC • Hand Movement subscale score	• Statistical power estimate based on other outcomes • Pre-registered data analysis NR
		Fine motor: Purdue Pegboard Test; Developmental Test of Visual-Motor Integration-III at 5y	Non-significant: All main effects Purdue Pegboard Test • Dominant Hand score • Non-Dominant Hand score  Developmental Test of Visual-Motor Integration-III • Motor component score	

## Visual development

### **Supplementation during pregnancy alone:**

#### *Summary:*

Five RCTs examined the effects of omega-3 fatty acid supplementation during pregnancy alone on visual development in the child (ages 1 day to 12 months)<sup>17,21,24,28,29</sup> (**Table 5**). All 5 studies found no effect of treatment on at least one measure of visual development among children assessed from the neonatal period through 12 months. Two RCTs found statistically significant, favorable effects of omega-3 fatty acid supplementation on one measure of visual acuity in the child at approximately age 2 months.<sup>17,24</sup>

#### *Assessment of the evidence<sup>xi</sup>:*

The evidence was characterized by mixed results, samples that may not reflect the diversity of the general U.S. population, and risk of bias due to deviations from the intended intervention and selection of the reported results (**Table 8**). Given these limitations, insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during pregnancy alone and visual development in the child and the body of evidence was rated 'grade not assignable.'

### **Supplementation during both pregnancy and lactation:**

#### *Summary:*

No studies examined the effects of omega-3 fatty acid supplementation during both pregnancy and lactation on visual development in the child, and therefore a grade was not assignable.

### **Supplementation during lactation alone:**

#### *Summary:*

One RCT examined the effect of omega-3 fatty acid supplementation during lactation alone on visual development in the child<sup>32,33</sup> (**Table 5**). Jensen et al reported unfavorable outcomes for a single, electrophysiological measure of visual acuity at ages 4 months and 8 months,<sup>33</sup> but no association with another electrophysiological measure at the same ages. Additional results revealed no association with other measures of visual development at ages 4 months, 8 months, and 5 years.<sup>32,33</sup>

#### *Assessment of the evidence:*

The entire body of evidence consisted of a single study with concerns regarding statistical power to detect effects in these secondary outcomes, risk of bias due to selection of reported results (**Table 8**), and a sample that may not reflect the diversity of the general U.S. population. Therefore, insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during lactation alone and visual development in the child, and the body of evidence was rated 'grade not assignable.'

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<sup>xi</sup> A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews> and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

**Table 5. Description of evidence on relationship between omega-3 fatty acid supplementation and visual development<sup>xii</sup>**

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<b>Pregnancy only</b>				
<p><b>Innis, 2008<sup>17</sup></b>  <b>Canada</b>  <b>N=135</b></p> <p>Mothers were age ~33y at enrollment, with ~77% ≥middle income, and ~76% completed university educated.                      Race/ethnicity: ~72% White.</p>	<p>400 mg/d DHA vs placebo (corn and soybean oils)                      16wk through delivery</p>	<p>Visual acuity: Teller Acuity Card at 60d</p>	<p><b>Significant:</b>  <b>Favors intervention</b>                      Lower visual acuity threshold                      Adj <math>\beta</math>: 1.215, Adj SE: 1.64, Adj OR: 3.37</p> <p>Non-significant:                      All other main effects</p> <ul style="list-style-type: none"> <li>• Acuity score (cycles/degree)</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear how many women started the study</li> <li>• Unclear whether missing data proportions/reasons differ by group</li> <li>• Pre-registered data analysis NR</li> </ul>
<p><b>Malcolm, 2003<sup>21</sup></b>  <b>UK</b>  <b>N=59</b></p> <p>Sample characteristics NR.</p>	<p>200 mg/d DHA fish oil vs placebo (oleic acid-rich sunflower)                      15wk through delivery</p>	<p>Visual acuity: Transient flash and pattern-reversal VEPs at 1-5d, 10wk, 6mo</p>	<p>Non-significant:                      All main effects                      Transient flash VEPs mean peak latency</p> <ul style="list-style-type: none"> <li>• N1</li> <li>• P1</li> <li>• N2</li> <li>• P2</li> <li>• N3</li> </ul>	<ul style="list-style-type: none"> <li>• Details of randomization and allocation NR</li> <li>• Most common reason for attrition during pregnancy: poor adherence</li> <li>• Pre-registered analysis plan NR</li> </ul>

<sup>xii</sup> Adj: adjusted; CI: confidence interval; DHA: docosahexaenoic acid; DOMInO: DHA to Optimize Mother Infant Outcome; EPA: eicosapentaenoic acid; NR: not reported; OR: odds ratio; POSGRAD: Prenatal Omega 3 Supplementation on child Growth and Development; RCT: randomized controlled trial; SE: standard error; VEP: visual evoked potentials

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p><b>Mulder, 2013<sup>24</sup></b>  <b>Canada</b>  <b>N=154</b></p> <p>Mothers were age ~33y at enrollment and 94.4% completed post-secondary education.  Race/Ethnicity: ~74% White.</p>	<p>400mg/d DHA vs placebo (corn and soybean oils)  16wk through delivery</p>	<p>Visual acuity: Teller Acuity Card at 2mo and 12mo</p>	<ul style="list-style-type: none"> <li>• No. of components (10wk and 6mo only)</li> </ul> <p>Pattern-reversal VEPs (10wk and 6mo only)</p> <ul style="list-style-type: none"> <li>• P100 peak latency</li> <li>• Threshold check size</li> </ul> <p><b>Significant:</b>  <b>Favors intervention</b></p> <p>Failure to achieve high visual acuity (2mo)  Adj P=0.03  Adj OR: 2.50, 95% CI: (1.02, 6.14)</p> <p>Non-significant:  Failure to achieve high visual acuity (12mo)</p>	<ul style="list-style-type: none"> <li>• No power calculation</li> <li>• Pre-registered data analysis outlined multiple regression, NR in paper</li> </ul>
<p><b>Smithers, 2011<sup>28</sup></b>  <b>Australia   DOMInO</b>  <b>N=182</b></p> <p>Mothers were age ~29y at enrollment and ~62% completed</p>	<p>800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo  18-21wk through delivery</p>	<p>Visual acuity: VEP-acuity; VEP-Latency  at 4mo</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>• Adjusted VEP acuity</li> <li>• Unadjusted VEP acuity</li> <li>• VEP latency</li> </ul>	<ul style="list-style-type: none"> <li>• Pre-registered analysis plan NR</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
secondary education. Race/ethnicity NR.			<ul style="list-style-type: none"> <li>○ 69 min of arc</li> <li>○ 48 min of arc</li> <li>○ 20 min of arc</li> </ul>	
<b>Stein, 2012<sup>29</sup></b> <b>Mexico   POSGRAD</b> <b>N=900</b>	400mg/d DHA vs placebo (corn and soybean oils) 18-22wk through delivery	Visual acuity: VEP at 3mo and 6mo	Non-significant: All main effects <ul style="list-style-type: none"> <li>● N1 latency</li> <li>● P1 latency</li> <li>● P1 amplitude</li> <li>● N3 latency</li> </ul>	<ul style="list-style-type: none"> <li>● Pre-registered analysis plan NR</li> </ul>
<b>Lactation only</b>				
<b>Jensen, 2005<sup>33</sup></b> <b>USA</b> <b>N=160</b>	200mg/d DHA vs placebo (corn and soybean oils) 5d through 4mo postpartum	Visual acuity: Transient VEP at 4mo and 8mo	<b>Significant:</b> <b>Favors control</b> VEP Amplitude, P<0.03 4mo Control (Mean± SD): 33.3± 12.42 Intervention: 28.9± 12.1  8mo, P<0.03 Control: 27.9± 11.02 Intervention: 24.3± 8.9  Non-significant: All other main effects <ul style="list-style-type: none"> <li>● VEP Latency</li> </ul>	<ul style="list-style-type: none"> <li>● Statistical power estimate based on other outcomes</li> <li>● Pre-registered data analysis NR</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
		Visual acuity: Teller Acuity Card at 4mo and 8mo	Non-significant: All main effects • Score (cycle/degree)	
		Visual acuity: Sweep VEP at 4mo	Non-significant: All main effects • Score (cycle/degree)	
<p><b>Jensen, 2010<sup>32</sup></b> <b>USA</b> <b>N=118</b></p> <p>Mothers were age ~32y at enrollment, with mean education 16y. Race/ethnicity of children: 79% White, ~14% Black, ~6% Hispanic.</p>	<p>200mg/d DHA vs placebo (corn and soybean oils) 5d through 4mo postpartum</p>	<p>Visual acuity: VEP at 5y</p>	<p>Non-significant: All main effects • VEP Amplitude, P=0.06 ○ Placebo &gt; DHA • VEP Latency • Sweep VEP acuity (cycle/degree)</p>	<ul style="list-style-type: none"> <li>• Statistical power estimate based on other outcomes</li> <li>• Pre-registered data analysis NR</li> </ul>
		<p>Visual acuity/Stereoacuity: Bailey-Lovie chart; Titmus Fly Stereotest at 5y</p>	<p>Non-significant: All main effects Bailey-Lovie chart • Right eye no. correct letters • Left eye no. correct letters</p> <p>Titmus Fly Stereotest • Smallest target identified</p>	

## **Social-emotional development**

### ***Supplementation during pregnancy alone:***

#### *Summary:*

Seven RCTs examined the effect of omega-3 fatty acid supplementation during pregnancy alone on social-emotional development in the child (ages 1 week to 7 years).<sup>6,7,11,12,18-20,22,25-27</sup> Two found statistically significant effects (**Table 6**).<sup>11,18,20</sup> In 1 study, children of mothers in the omega-3 fatty acid supplemented group were more likely to have higher total difficulties or hyperactivity on a parent-reported measure of child behavior at 4 years, but supplementation had no effect on other parameters measured with the same tool.<sup>20</sup> At 7 years, using an age-appropriate version of the same tool, the authors reported that the total score indicated unfavorable outcomes for children of mothers in the supplemented group.<sup>11</sup> Another study revealed that omega-3 fatty acid supplementation resulted in a more attenuated (favorable) stress response at 3 months.<sup>18</sup> The remaining studies did not report any statistically significant results.<sup>6,7,12,22,25-27</sup>

#### *Assessment of the evidence<sup>xiii</sup>:*

Given the mixed results and concerns regarding the risk of bias due to parent-reported outcomes (**Table 8**), insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during pregnancy alone and social-emotional development in the child, and therefore the body of evidence was rated ‘grade not assignable.’

### ***Supplementation during both pregnancy and lactation:***

#### *Summary:*

One RCT reported no effect of omega-3 fatty acid supplementation during both pregnancy and lactation on a parent-reported measure of social-emotional development in the child at age 4 years and 5 years (**Table 6**).<sup>1</sup>

#### *Assessment of the evidence:*

The entire body of evidence consisted of a single study with concerns regarding statistical power to detect effects in these secondary outcomes, risk of bias concerns due to parent-reported outcomes (Table 8), and limited information on the generalizability of results to the general U.S. population. Therefore, insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation and social-emotional development in the child, and the body of evidence was rated ‘grade not assignable.’

### ***Supplementation during lactation alone:***

#### *Summary:*

No studies examined the effect of omega-3 fatty acid supplementation during lactation alone on social-emotional development in the child, and therefore a grade was not assignable.

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<sup>xiii</sup> A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews> and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

**Table 6. Description of evidence on relationship between omega-3 fatty acid supplementation and social-emotional development<sup>xiv</sup>**

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<b>Pregnancy only</b>				
<b>Colombo, 2019<sup>6</sup></b> <b>USA</b> <b>N=161</b>  Mothers were age ~26y at enrollment, with mean income <\$46K and ~14y education. Race/Ethnicity: 6% Hispanic, 31% Black.	600 mg/d DHA vs placebo (corn and soybean oils) ~14.5wk through delivery	Behavior--Parent reported: BASC at 36mo, 48mo, 60mo, 72mo	Non-significant: All main effects <ul style="list-style-type: none"> <li>• Externalizing Problems</li> <li>• Internalizing Problems</li> <li>• Behavioral Symptoms</li> <li>• Adaptive Skills</li> </ul>	<ul style="list-style-type: none"> <li>• Results parent-reported</li> <li>• More outcomes reported in the paper than on the clinical trials registry</li> <li>• Pre-registered data analysis plan NR</li> </ul>
<b>Dunstan, 2008<sup>7</sup></b> <b>Australia</b> <b>N=72</b>  Mothers were age ~32y at enrollment and ~73% completed ≥12y education. Race/Ethnicity: 100% White.	2.2g/d DHA + 1.1 g/d EPA vs placebo (olive oil) 20wk through delivery	Behavior--Parent Reported: CBCL: 1.5–5y at 2.5y	Non-significant: All main effects <ul style="list-style-type: none"> <li>• Internalizing scale</li> <li>• Externalizing scale</li> <li>• Total problem behavioral scale</li> </ul>	<ul style="list-style-type: none"> <li>• Results parent-reported</li> <li>• Probable differences in reasons for attrition, no power calculation for neurobehavioral results</li> <li>• Pre-registered data analysis plan NR</li> </ul>
<b>Gould, 2017<sup>11</sup></b> <b>Australia   DOMInO</b> <b>N=543</b>	800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo 18-21wk through delivery	Behavior--Parent reported: SDQ at 7y	<b>Significant:</b> <b>Favors control</b> Total difficulties score Adj P=0.02 Ref: Control	<ul style="list-style-type: none"> <li>• Results parent-reported</li> </ul>

<sup>xiv</sup> Adj: adjusted; ASQ: Ages and Stages Questionnaire; BASC: Behavioral Assessment System for Children; BSID: Bayley Scales of Infant Development; CBCL: Child Behavior Checklist; CI: confidence interval; DHA: docosahexaenoic acid; DOMInO: DHA to Optimize Mother Infant Outcome; EPA: eicosapentaenoic acid; ETA: eicosatetraenoic acid; FFSF: Face-to-Face Still-Face task; INFAT: The Impact of the Nutritional Fatty Acids During Pregnancy and Lactation for Early Human Adipose Tissue Development; NBAS: Neonatal Behavioral Assessment Scale; NR: not reported; POSGRAD: Prenatal Omega 3 Supplementation on child Growth and Development; RCT: randomized controlled trial; SDQ: Strengths and Difficulties Questionnaire

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<p>Mothers were age ~30y at enrollment and ~66% completed secondary education. Race/ethnicity NR.</p>			<p>Adj Mean Difference: 1.09, 95% CI: (0.18, 2.00)</p>	
<p><b>Gustafson, 2013<sup>12</sup></b> <b>USA</b> <b>N=44</b></p> <p>Mothers were age ~26y at enrollment and completed ~14y education. Race/Ethnicity: 37.3% Black, 46.3% White, 13.4% Hispanic, 3% Asian.</p>	<p>600 mg/d DHA vs placebo (corn and soybean oils) 12-20wk through delivery</p>	<p>NBAS: State organization, State regulation scales at 1wk</p>	<p>Non-significant: All main effects</p> <ul style="list-style-type: none"> <li>• State organization</li> <li>• State regulation scales</li> </ul>	<ul style="list-style-type: none"> <li>• No power calculation</li> <li>• Pre-registered analysis plan NR</li> </ul>
<p><b>Keenan, 2016<sup>18</sup></b> <b>USA</b> <b>N=49</b></p> <p>Age 20-30y. 100% Medicaid eligible. Race/Ethnicity: 100% Black.</p>	<p>450 mg/d DHA + 40 mg/d DPA + 40 mg/d ETA + 90 mg/d EPA + 10 mg/d Vitamin E vs 990 mg/d soybean oil + 16.5 mg/d Vitamin E + 10 mg/d EPA + 10 mg/d DHA 16-21wk for 6wk</p>	<p>Behavior--Stress reactivity: FFSS cortisol response at 3mo</p>	<p><b>Significant:</b> <b>Favors intervention</b> Adj P=0.018 F=5.36</p>	<ul style="list-style-type: none"> <li>• Reasons for missingness by group NR</li> <li>• Pre-registered data analysis plan NR</li> </ul>
<p><b>Makrides, 2010<sup>19</sup></b> <b>Australia   DOMInO</b> <b>N=694</b></p> <p>Mothers were age ~29y at enrollment and ~68% completed more than secondary education. Race/ethnicity NR.</p>	<p>800mg/d DHA + 100 mg/d EPA vs Vegetable oil placebo 18-21wk through delivery</p>	<p>BSID-III: Social-emotional scale Adaptive Behavioral subscales at 18mo</p>	<p>Non-significant: All main effects</p> <ul style="list-style-type: none"> <li>• Social-emotional Standardized Score</li> <li>• Adaptive Behavior Standardized Score</li> </ul>	<ul style="list-style-type: none"> <li>• Pre-registered analysis plan NR</li> </ul>
<p><b>Makrides, 2014<sup>20</sup></b> <b>Australia   DOMInO</b> <b>N=646</b></p>	<p>800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo</p>	<p>Behavior--Parent Reported: SDQ scales, subscales at 4y</p>	<p><b>Significant:</b> <b>Favors control</b> Total difficulties</p>	<ul style="list-style-type: none"> <li>• Results parent-reported</li> <li>• Pre-registered analysis plan NR</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
Mothers were age ~29y at enrollment and ~68% completed more than secondary education. Race/ethnicity NR.	18-21wk through delivery		Adj P=0.04 Ref: Control Adj Mean Difference: 0.63, 95% CI: (0.03, 1.23)  Hyperactivity Adj P=0.04 Ref: Control Adj Mean Difference: 0.30, 95% CI: (0.01, 0.59)	
<b>Meldrum, 2015<sup>22</sup></b> <b>Australia</b> <b>N=48</b>  Mothers were age ~32y at enrollment and ~73% completed ≥12y education. Race/Ethnicity: 100% White.	2.2g/d DHA + 1.1 g/d EPA vs placebo (olive oil) 20wk through delivery	Behavior--Parent, Child Reported: CBCL at 12y	Non-significant: All main effects Parent-Report <ul style="list-style-type: none"> <li>• Internalizing Behaviors</li> <li>• Externalizing Behaviors</li> <li>• Total Behaviors score</li> <li>• Total Competence score</li> </ul>	<ul style="list-style-type: none"> <li>• Results parent-reported</li> <li>• Among those followed to 12y, birth weight differed by treatment group</li> <li>• Possible differences in reasons for attrition</li> <li>• No power calculation, Likely under-powered</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
			Child-Self Report <ul style="list-style-type: none"> <li>• Internalizing Behaviors</li> <li>• Externalizing Behaviors</li> <li>• Total Behaviors score</li> <li>• Total Competence score</li> </ul>	
<b>Ostadrahimi, 2018<sup>25</sup></b> <b>Iran</b> <b>N=146</b>  Mothers were age ~26y at enrollment and ~8% completed >12y education. ~19% had non-adequate family income. Race/ethnicity NR.	120mg/d DHA + 180mg/d EPA vs placebo (liquid paraffin) 16-20wk through delivery	Behavior--Parent reported: ASQ-2 Personal-social subscale at 4mo and 6mo	Non-significant: All main effects <ul style="list-style-type: none"> <li>• Mean score</li> <li>• Subnormal development</li> </ul>	<ul style="list-style-type: none"> <li>• Behavioral data parent-reported data</li> <li>• Pre-registered analysis plan NR</li> </ul>
<b>Ramakrishnan, 2015<sup>27</sup></b> <b>Mexico   POSGRAD</b> <b>N=730</b>  Mothers were age ~26y at enrollment and ~59% completed ≥12y education.	400mg/d DHA vs placebo (corn and soybean oils) 18-22wk through delivery	BSID-II: Behavior Rating Scale at 18mo	Non-significant: All main effects <ul style="list-style-type: none"> <li>• Mean score</li> <li>• Risk of delay</li> </ul>	<ul style="list-style-type: none"> <li>• Results parent-reported</li> <li>• Pre-registered data analysis NR</li> </ul>
<b>Ramakrishnan, 2016<sup>26</sup></b> <b>Mexico   POSGRAD</b> <b>N=797</b>  Mothers were age ~26y at enrollment and ~58% completed ≥12y education.	400mg/d DHA vs placebo (corn and soybean oils) 18-22wk through delivery	Behavior--Parent Reported: BASC-2 at 5y	Non-significant: All main effects <ul style="list-style-type: none"> <li>• Externalizing problems composite               <ul style="list-style-type: none"> <li>○Hyperactivity</li> <li>○Aggression</li> </ul> </li> <li>• Internalizing problems composite               <ul style="list-style-type: none"> <li>○Anxiety</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Results parent-reported</li> <li>• Pre-registered data analysis NR</li> </ul>

Study and Participant Characteristics	Intervention (All RCTs)	Outcome(s)	Results	Limitations
<ul style="list-style-type: none"> <li>○ Depression</li> <li>○ Somatization</li> <li>● Adaptive skills composite</li> <li>○ Withdrawal</li> <li>○ Adaptability</li> <li>○ Activities in daily life</li> <li>○ Atypicality</li> <li>○ Attention problems</li> <li>○ Functional communication</li> <li>○ Social skills</li> <li>● Behavioral Symptoms Index</li> <li>○ Anger control</li> <li>○ Bullying</li> <li>○ Developmental and social disorders</li> <li>○ Emotional self-control</li> <li>○ Executive functioning</li> <li>○ Negative emotionality</li> <li>○ Resiliency</li> </ul>				
<b>Pregnancy and Lactation</b>				
<p><b>Brei, 2017<sup>1</sup></b>  <b>Germany   INFAT</b>  <b>N=130</b></p> <p>Mothers were age ~33y at enrollment and 73% completed ≥12y education. Race/Ethnicity: NR.</p>	<p>1020 mg/d DHA + 180 mg/d EPA + 9 mg/d Vitamin E vs general nutrition advice</p> <p>15wk gestation through 4mo postpartum</p>	<p>Behavior--Parent reported: Child Development Inventory: Social, self-help scales</p> <p>at 4y and 5y</p>	<p>Non-significant:  All main effects</p> <ul style="list-style-type: none"> <li>● Social scale classification (Normal, Borderline, Delay)</li> <li>● Self help scale classification (Normal, Borderline, Delay)</li> </ul>	<ul style="list-style-type: none"> <li>● Reasons for missingness by group NR</li> <li>● Results were parent-reported</li> <li>● Pre-registered data analysis NR</li> </ul>

## **Academic performance**

### ***Supplementation during pregnancy alone:***

#### *Summary:*

A single RCT examined the effect of omega-3 fatty acid supplementation during pregnancy alone on academic performance in the child and found no effect on a measure of reading, spelling, and math computation at age 7 years (**Table 7**).<sup>11</sup>

#### *Assessment of the evidence<sup>xv</sup>:*

The entire body of evidence consisted of a single study in a sample that may not reflect the diversity of the general U.S. population. Therefore, insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during pregnancy alone and academic performance in the child, and the body of evidence was rated 'grade not assignable.'

### ***Supplementation during both pregnancy and lactation:***

#### *Summary:*

No studies examined the effect of omega-3 fatty acid supplementation during both pregnancy and lactation on academic performance in the child, and therefore a grade was not assignable.

### ***Supplementation during lactation alone:***

#### *Summary:*

No studies examined the effect of omega-3 fatty acid supplementation during lactation alone on academic performance in the child, and therefore a grade was not assignable.

## **Anxiety**

#### *Summary:*

No studies examined the effect of omega-3 fatty acid supplementation during pregnancy and/or lactation on anxiety in the child, and therefore a grade was not assignable.

## **Depression**

#### *Summary:*

No studies examined the effect of omega-3 fatty acid supplementation during pregnancy and/or lactation on depression in the child, and therefore a grade was not assignable.

## **ADD/ADHD**

### ***Supplementation during pregnancy alone:***

#### *Summary:*

A single RCT examined the effect of omega-3 fatty acid supplementation during pregnancy alone on risk of ADD/ADHD in the child. The results showed no effect at age 4 years,<sup>10</sup>

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<sup>xv</sup> A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews> and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

and a higher risk of ADHD among children of mothers in the treatment group at 7 years (**Table 7**).<sup>11</sup>

*Assessment of the evidence:*

The entire body of evidence consisted of a single study in a sample that may not reflect the diversity of the general U.S. population. Therefore, insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during pregnancy alone and ADD/ADHD in the child, and a grade was not assignable.

***Supplementation during both pregnancy and lactation:***

*Summary:*

No studies examined the effect of omega-3 fatty acid supplementation during both pregnancy and lactation on risk of ADD/ADHD in the child, and therefore a grade was not assignable.

***Supplementation during lactation alone:***

*Summary:*

No studies examined the effect of omega-3 fatty acid supplementation during lactation alone on risk of ADD/ADHD in the child, and therefore a grade was not assignable.

**Autism spectrum disorder**

***Supplementation during pregnancy alone:***

*Summary:*

One RCT<sup>10</sup> and 1 PCS<sup>16</sup> examined the effect of omega-3 fatty acid supplementation during pregnancy alone on risk of autism spectrum disorder in the child (ages 36 months to 4 years), and neither study reported a statistically significant relationship (**Table 7**).

*Assessment of the evidence:*

Given the small number of studies in samples that may not reflect the diversity of the general U.S. population, as well as concerns regarding risk of bias due to confounding, classification of exposures, and the selection of reported results (**Table 9**), insufficient evidence existed to determine the relationship between omega-3 fatty acid supplementation during pregnancy alone and autism spectrum disorder in the child, and therefore a grade was not assignable.

***Supplementation during both pregnancy and lactation:***

*Summary:*

No studies examined the effect of omega-3 fatty acid supplementation during both pregnancy and lactation on risk of autism spectrum disorder in the child, and therefore a grade was not assignable.

***Supplementation during lactation alone:***

*Summary:*

No studies examined the effect of omega-3 fatty acid supplementation during lactation alone on risk of autism spectrum disorder in the child, and therefore a grade was not assignable.

**Table 7. Description of evidence on relationship between omega-3 fatty acid supplementation and academic performance, risk of ADD/ADHD, or risk of Autism spectrum disorder<sup>xvi</sup>**

Study and Participant Characteristics	Intervention/Exposure	Outcome(s)	Results	Limitations
<b>Pregnancy Only</b>				
<b>Academic Performance</b>				
<b>Gould, 2017<sup>11</sup>   RCT</b> <b>Australia   DOMInO</b> <b>N=543</b>  Mothers were age ~30y at enrollment and ~66% completed secondary education. Race/ethnicity NR.	800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo 18-21wk through delivery	WRAT-4 at 7y	Non-significant: All main effects • Word reading • Spelling • Math computation	• No major limitations
<b>ADD/ADHD</b>				
<b>Gould, 2017<sup>11</sup>   RCT</b> <b>Australia   DOMInO</b> <b>N=543</b>  Mothers were age ~30y at enrollment and ~66% completed secondary education. Race/ethnicity NR.	Average supplemental Omega-3 (100 mg/d) 1mo through delivery	ADHD score Conners 3 AI-parent at 7y	<b>Significant:</b> <b>Favors control</b> ADHD score Adj P=0.02 Ref: Control Adj Mean Difference: 2.84, 95% CI: (0.38, 5.30)	• No major limitations
<b>Makrides, 2014<sup>20</sup>   RCT</b> <b>Australia   DOMInO</b> <b>N=646</b>	800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo 18-21wk through delivery	Hyperactivity disorders: No methodological details at 4y	Non-significant: • All main effects Diagnosis	• No methodological details for hyperactivity disorders • Pre-registered analysis plan NR

<sup>xvi</sup> ADD: attention deficit disorder; ADHD: attention-deficit/hyperactivity disorder; Adj: adjusted; ASD: autism spectrum disorder; CI: confidence interval; DHA: docosahexaenoic acid; DOMInO: DHA to Optimize Mother Infant Outcome; EPA: eicosapentaenoic acid; MARBLES: Markers of Autism Risk in Babies-Learning Early Signs; NR: not reported; PCS: prospective cohort study; RCT: randomized controlled trial; WRAT-4: Wide Range Achievement Test Fourth Edition

Study and Participant Characteristics	Intervention/Exposure	Outcome(s)	Results	Limitations
<p>Mothers were age ~29y at enrollment and ~68% completed more than secondary education. Race/ethnicity NR.</p>				
<b>Autism Spectrum Disorder</b>				
<p><b>Makrides, 2014<sup>20</sup>   RCT</b> <b>Australia   DOMInO</b> <b>N=646</b></p>	<p>800mg/d DHA + 100 mg/d EPA vs Vegetable oil (rapeseed, sunflower, and palm) placebo 18-21wk through delivery</p>	<p>ASD diagnosis at 4y</p>	<p>Non-significant: All main effects • Diagnosis</p>	<ul style="list-style-type: none"> <li>• No methodological details for ASD diagnosis</li> <li>• Pre-registered analysis plan NR</li> </ul>
<p>Mothers were age ~29y at enrollment and ~68% completed more than secondary education. Race/ethnicity NR.</p>				
<p><b>Huang, 2020<sup>16</sup>   PCS</b> <b>USA   MARBLES</b> <b>N=258</b></p>	<p>Omega-3 supplement intake (100 mg/d increments) 1mo-9mo</p>	<p>ASD diagnosis: Mullen Scales of Early Learning, Autism Diagnostic Observation Schedule at 36mo</p>	<p>Non-significant: All main effects • Diagnosis</p>	<ul style="list-style-type: none"> <li>• Multiple key confounders not accounted for</li> <li>• Critical co-exposures NR</li> <li>• No information on missing outcome data, but other missing data appears to be balanced across groups</li> <li>• Pre-registered data analysis plan NR</li> </ul>
<p>Mothers were age ~34y at enrollment and ~59% completed ≥Bachelor's degree. Race/ethnicity: ~55% White.</p>				

**Table 8. Risk of bias for randomized controlled trials examining omega-3 fatty acid supplementation and developmental milestones, including neurocognitive development, in the child<sup>xvii xviii</sup>**

	Randomization	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of the reported result
Brei, 2017 <sup>1</sup>	Low	Low	Some concerns	High	Some concerns
Campoy, 2011 <sup>2</sup>	Low	Low	Low	Low	Some concerns
Catena, 2016 <sup>4</sup>	Low	Low	Low	Low	High
Catena, 2019 <sup>3</sup>	Low	Low	Low	Low	Some concerns
Colombo, 2016 <sup>5</sup>	Low	Low	High	Low	Some concerns
Colombo, 2019 <sup>6</sup>	Low	Low	Low	Low	Some concerns
Dunstan, 2008 <sup>7</sup>	Low	Low	Some concerns	Low	Some concerns
Escolano-Margarit, 2011 <sup>8</sup>	Low	Low	Low	Some concerns	Some concerns
Gould, 2014 <sup>10</sup>	Low	Low	Low	Low	Some concerns
Gould, 2016 <sup>9</sup>	Low	Low	Some concerns	Low	Some concerns
Gould, 2017 <sup>11</sup>	Low	Low	Low	Low	Low
Gustafson, 2013 <sup>12</sup>	Low	Low	Low	Low	Some concerns
Helland, 2001 <sup>13</sup>	Some concerns	High	Some concerns	Low	Some concerns
Helland, 2003 <sup>15</sup>	Some concerns	High	Some concerns	Low	Some concerns
Helland, 2008 <sup>14</sup>	Some concerns	High	Some concerns	Low	Some concerns
Innis, 2008 <sup>17</sup>	Low	Low	Some concerns	Low	Some concerns
Jensen, 2005 <sup>33</sup>	Low	Low	Low	Low	Some concerns
Jensen, 2010 <sup>32</sup>	Low	Low	Low	Low	Some concerns
Keenan, 2016 <sup>18</sup>	Low	Low	Some concerns	Low	Some concerns
Makrides, 2010 <sup>19</sup>	Low	Low	Low	Low	Some concerns
Makrides, 2014 <sup>20</sup>	Low	Low	Low	Low	Some concerns
Malcolm, 2003 <sup>21</sup>	Some concerns	High	Low	Low	Some concerns
Meldrum, 2015 <sup>22</sup>	Low	Low	Some concerns	Low	Some concerns
Mulder, 2013 <sup>24</sup>	Low	Low	Low	Low	High
Mulder, 2018 <sup>23</sup>	Low	Low	Low	Low	Some concerns
Ostadrahimi, 2018 <sup>25</sup>	Low	Low	Low	Low	Some concerns
Ramakrishnan, 2015 <sup>27</sup>	Low	Low	Low	Low	Some concerns
Ramakrishnan, 2016 <sup>26</sup>	Low	Low	Low	Low/High	Some concerns

<sup>xvii</sup> A detailed description of the methodology used for assessing risk of bias is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews> and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

<sup>xviii</sup> Possible ratings of low, some concerns, or high determined using the "[Cochrane Risk-of-bias 2.0](#)" (RoB 2.0) (August 2016 version)" (Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). *Cochrane Methods. Cochrane Database of Systematic Reviews* 2016, Issue 10 (Suppl 1). [dx.doi.org/10.1002/14651858.CD201601](https://doi.org/10.1002/14651858.CD201601).)

Smithers, 2011 <sup>28</sup>	Low	Low	Low	Low	Some concerns
Stein, 2012 <sup>29</sup>	Low	Low	Low	Low	Some concerns
van Goor, 2010 <sup>30</sup>	Some concerns	Low	Low	Low	Some concerns
van Goor, 2011 <sup>31</sup>	Some concerns	Low	Low	Some concerns	Some concerns

**Table 9. Risk of bias for observational studies examining omega-3 fatty acid supplementation and developmental milestones, including neurocognitive development, in the child<sup>xix</sup>**

	Confounding	Selection of participant	Classification of exposures	Deviations from intended exposures	Missing data	Outcome measurement	Selection of the reported result
Huang, 2020 <sup>16</sup>	Serious	Moderate	Serious	No Information	No Information	Moderate	Serious

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<sup>xix</sup> Possible ratings of low, moderate, serious, critical, or no information determined using the "Risk of Bias for Nutrition Observational Studies" tool (RoB-NObs) (Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.)

## Research recommendations

- Strive to include participants who are reflective of the U.S. population on characteristics such as race/ethnicity, socioeconomic background, age, etc.
- Research is needed to determine whether the magnitude and/or direction of effects differ when omega-3 fatty acids are consumed as an individual nutrient supplement during pregnancy and/or lactation versus as in combination with a multi-vitamin/mineral supplement or in fortified foods, in relation to neurobehavioral development in the child.
- More research is needed to understand the relationship between omega-3 fatty acid supplementation during pregnancy and/or lactation and cognitive, language, motor, visual, and social-emotional development in the child. In particular, research should consider the baseline omega-3 fatty acid status of the mother and usual intakes in the U.S. population.
- More research is needed to understand the relationship between omega-3 fatty acid supplementation during pregnancy and/or lactation and academic performance in the child. In particular, research should consider the maternal baseline omega-3 fatty acid status and usual intakes in the U.S. population.
- More research is needed to understand the relationship between omega-3 fatty acid supplementation during pregnancy and/or lactation and risk of anxiety, depression, ADD/ADHD, and autism spectrum disorder in the child. In particular, research should consider the maternal baseline omega-3 fatty acid status and usual intakes in the U.S. population.
- Research is needed to understand the relationship between omega-3 fatty acid supplementation during pregnancy and/or lactation and risk of maternal anxiety and depression. In particular, research should consider the maternal baseline omega-3 fatty acid status and usual intakes in the U.S. population.
- Additional research is needed to better identify the time period(s) during pregnancy and/or lactation when an effect of omega-3 fatty acid supplementation on child development is more likely to be observed. Specifically, more studies are needed to investigate the effect of supplementation during both pregnancy and lactation, and during lactation alone on child development.
- Further research is needed to determine whether there are differential effects of the various forms of omega-3 fatty acid supplements during pregnancy and/or lactation on child development.

## Included articles

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## METHODOLOGY

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The NESR team used its rigorous, protocol-driven methodology to support the 2020 Dietary Guidelines Advisory Committee in conducting this systematic review.

NESR's systematic review methodology involves:

- Developing a protocol,
- Searching for and selecting studies,
- Extracting data from and assessing the risk of bias of each included study,
- Synthesizing the evidence,
- Developing conclusion statements,
- Grading the evidence underlying the conclusion statements, and
- Recommending future research.

A detailed description of the methodology used in conducting this systematic review is available on the NESR website: <https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews>, and can be found in the 2020 Dietary Guidelines Advisory Committee Report, Part C: Methodology.<sup>xx</sup> This systematic review was peer reviewed by Federal scientists, and information about the peer review process can also be found in the Committee's Report, Part C. Methodology. Additional information about this systematic review, including a description of and rationale for any modifications made to the protocol can be found in the 2020 Dietary Guidelines Advisory Committee Report, Chapter 2. Food, Beverage, and Nutrient Consumption During Pregnancy and Chapter 3. Food, Beverage, and Nutrient Consumption During Lactation.

Below are details of the final protocol for the systematic review described herein, including the:

- Analytic framework
- Literature search and screening plan
- Literature search and screening results

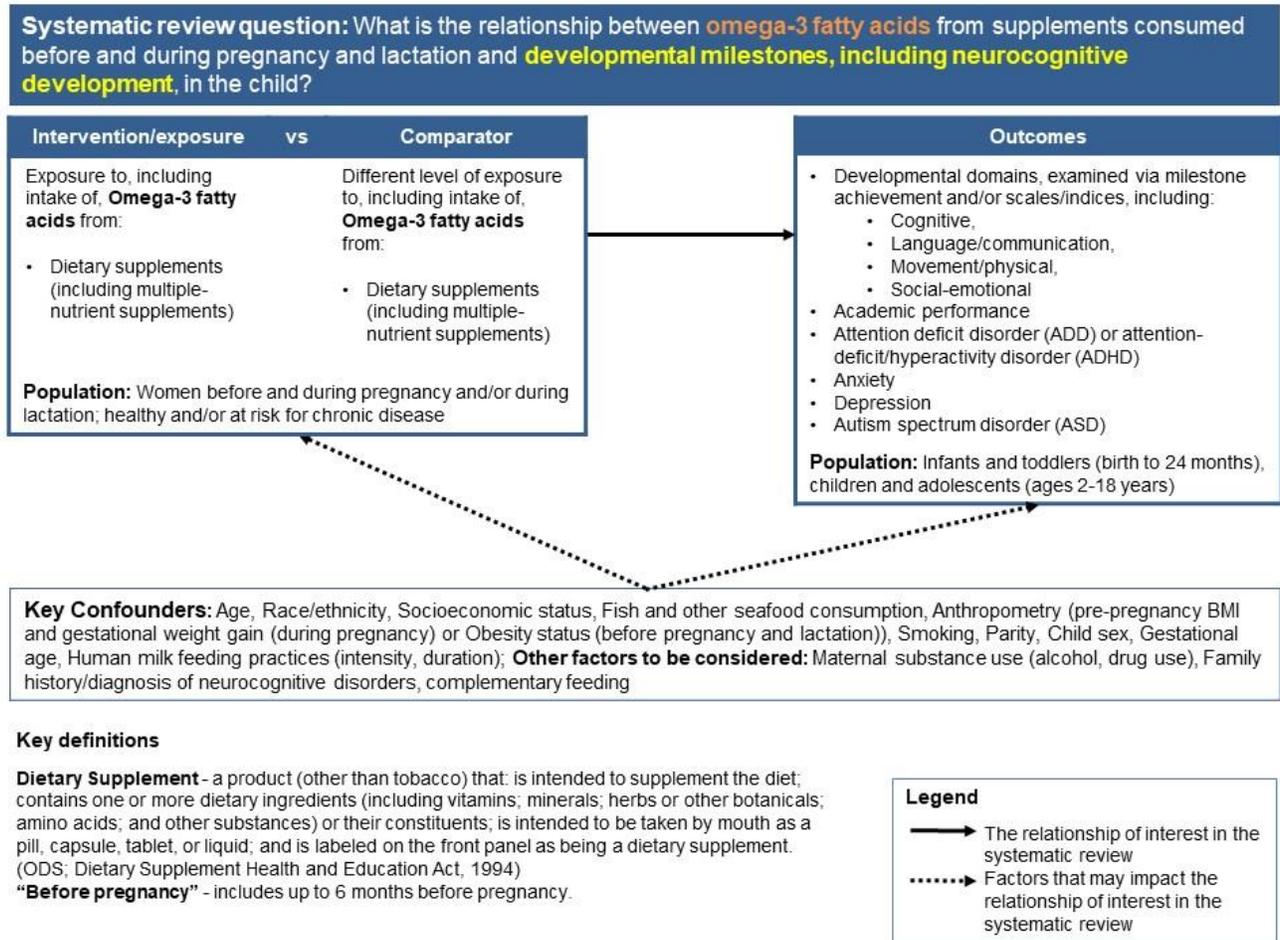
## ANALYTIC FRAMEWORK

The analytic framework (**Figure 1**) illustrates the overall scope of the systematic review, including the population, the interventions and/or exposures, comparators, and outcomes of interest. It also includes definitions of key terms and identifies key confounders considered in the systematic review. The inclusion and exclusion criteria that follow provide additional information about how parts of the analytic framework were defined and operationalized for the review.

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<sup>xx</sup> Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

**Figure 1: Analytic framework**



## LITERATURE SEARCH AND SCREENING PLAN

### Inclusion and exclusion criteria

This table provides the inclusion and exclusion criteria for the systematic review. The inclusion and exclusion criteria are a set of characteristics used to determine which articles identified in the literature search were included in or excluded from the systematic review.

**Table 10. Inclusion and exclusion criteria**

<b>Category</b>	<b>Inclusion Criteria</b>	<b>Exclusion Criteria</b>
<b>Study design</b>	<ul style="list-style-type: none"> <li>• Randomized controlled trials</li> <li>• Non-randomized controlled trials including quasi-experimental and controlled before-and-after studies</li> <li>• Prospective cohort studies</li> <li>• Retrospective cohort studies</li> <li>• Nested case-control studies</li> </ul>	<ul style="list-style-type: none"> <li>• Uncontrolled trials</li> <li>• Case-control studies</li> <li>• Uncontrolled before-and-after studies</li> <li>• Cross-sectional studies</li> <li>• Narrative reviews</li> <li>• Systematic reviews</li> <li>• Meta-analyses</li> </ul>
<b>Intervention/exposure</b>	<ul style="list-style-type: none"> <li>• Exposure to, including intake of, Omega-3 fatty acids from:               <ul style="list-style-type: none"> <li>○ Dietary supplements (including multiple-nutrient supplements)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Exposure to multiple-micronutrient supplements in which nutrients other than the nutrient of interest vary</li> </ul>
<b>Comparator</b>	<ul style="list-style-type: none"> <li>• Different levels of exposure to, including intake of, Omega-3 fatty acids from:               <ul style="list-style-type: none"> <li>○ Dietary supplements (including multiple-nutrient supplements)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• No comparator</li> <li>• Exposure to multiple-micronutrient supplements in which nutrients other than the nutrient of interest vary</li> </ul>
<b>Outcome: Developmental milestones, including neurocognitive health</b>	<ul style="list-style-type: none"> <li>• Developmental domains, examined via milestone achievement and/or scales/indices, including:               <ul style="list-style-type: none"> <li>○ Cognitive,</li> <li>○ Language/communication,</li> <li>○ Movement/physical,</li> <li>○ Social-emotional</li> </ul> </li> <li>• Academic performance</li> <li>• Attention deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD)</li> <li>• Anxiety</li> <li>• Depression</li> <li>• Autism spectrum disorder (ASD)</li> </ul>	<ul style="list-style-type: none"> <li>• N/A</li> </ul>

Category	Inclusion Criteria	Exclusion Criteria
<b>Date of publication</b>	<ul style="list-style-type: none"> <li>January 1980 – February 2020</li> </ul>	<ul style="list-style-type: none"> <li>Articles published prior to January 1980</li> </ul>
<b>Publication status</b>	<ul style="list-style-type: none"> <li>Articles that have been peer-reviewed</li> </ul>	<ul style="list-style-type: none"> <li>Articles that have not been peer-reviewed and are not published in peer-reviewed journals, including unpublished data, manuscripts, reports, abstracts, and conference proceedings</li> </ul>
<b>Language of publication</b>	<ul style="list-style-type: none"> <li>Articles published in English</li> </ul>	<ul style="list-style-type: none"> <li>Articles published in languages other than English</li> </ul>
<b>Country<sup>xxi</sup></b>	<ul style="list-style-type: none"> <li>Studies conducted in countries ranked as high or very high human development</li> </ul>	<ul style="list-style-type: none"> <li>Studies conducted in countries ranked as medium or lower human development</li> </ul>
<b>Study participants</b>	<ul style="list-style-type: none"> <li>Human participants</li> </ul>	<ul style="list-style-type: none"> <li>Non-human participants (e.g., animal or in-vitro models)</li> <li>Studies that <i>exclusively</i> enroll women who became pregnant using Assisted Reproductive Technologies</li> <li>Studies that <i>exclusively</i> enroll women with multiple gestation pregnancies</li> <li>Studies that enroll both singleton and multiple pregnancies and do not account for singleton and multiple gestation in the design or analyses and only present aggregate findings</li> </ul>

<sup>xxi</sup>The Human Development classification was based on the Human Development Index (HDI) ranking from the year the study intervention occurred or data were collected (UN Development Program. HDI 1990-2017 HDRO calculations based on data from UNDESA (2017a), UNESCO Institute for Statistics (2018), United Nations Statistics Division (2018b), World Bank (2018b), Barro and Lee (2016) and IMF (2018). Available from: <http://hdr.undp.org/en/data>). If the study did not report the year in which the intervention occurred or data were collected, the HDI classification for the year of publication was applied. HDI values are available from 1980, and then from 1990 to present. If a study was conducted prior to 1990, the HDI classification from 1990 was applied. If a study was conducted in 2018 or 2019, the most current HDI classification was applied. When a country was not included in the HDI ranking, the current country classification from the World Bank was used instead (The World Bank. World Bank country and lending groups. Available from: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-country-and-lending-groups>).

Category	Inclusion Criteria	Exclusion Criteria
<b>Life stage of study participants - intervention or exposure</b>	<ul style="list-style-type: none"> <li>• Women up to 6 months before pregnancy</li> <li>• Women during pregnancy</li> <li>• Women during lactation</li> </ul>	<ul style="list-style-type: none"> <li>• N/A</li> </ul>
<b>Life stage of study participants - outcomes</b>	<ul style="list-style-type: none"> <li>• Infants and toddlers (birth – 24 months)</li> <li>• Children and adolescents (2 – 18 years)</li> </ul>	<ul style="list-style-type: none"> <li>• Adults (19 – 64 years)</li> <li>• Older adults (65 years and older)</li> </ul>
<b>Health status of study participants</b>	<ul style="list-style-type: none"> <li>• Studies that enroll participants who are healthy and/or at risk for chronic disease, including those with obesity</li> <li>• Studies that enroll <b>some</b> participants diagnosed with a disease or with the health outcome of interest: <ul style="list-style-type: none"> <li>○ Neurocognitive disorders (ADD, ADHD, anxiety, depression, or ASD)</li> <li>○ Studies that enroll some participants who are deficient in omega-3 fatty acids</li> </ul> </li> <li>• Studies that enroll <b>some</b> mothers with infants who are born preterm (&lt;37 weeks and 0/7 days gestational age)</li> <li>• Studies that <b>exclusively</b> enroll or <b>enroll some</b> mothers diagnosed with the outcome of interest that is to be examined in the infant/child (developmental milestones, including neurocognitive development)</li> </ul>	<ul style="list-style-type: none"> <li>• Studies that <b>exclusively</b> enroll participants diagnosed with a disease, or hospitalized with an illness or injury. (For this criterion, studies that exclusively enroll participants with obesity will not be excluded.)</li> <li>• Studies that <b>exclusively</b> enroll participants with the outcome of interest (i.e., studies that aim to treat participants who have already been diagnosed with the outcome of interest)</li> <li>• Studies that <b>exclusively</b> enroll infants born preterm (gestational age &lt;37 weeks and 0/7 days), infants with low birth weight (&lt;2500g), and/or infants born small for gestational age</li> </ul>

## Electronic databases and search terms

### PubMed

- Provider: U.S. National Library of Medicine
- Date(s) Searched: February 5, 2020
- Date range searched: January 1, 1980 – February 5, 2020
- Search Terms:

**#1** - "Fatty Acids, Omega-3"[Mesh] OR omega-3[tiab] OR N-3 fat\*[tiab] OR N-3 polyunsat\*[tiab] OR PUFA\*[tiab] OR linolenic [tiab] OR eicosapentaenoic [tiab] OR EPA[tiab] OR docosahexaenoic acid\*[tiab] OR DHA[tiab] OR ((fat [tiab] OR fats[tiab] OR fatty[tiab]) AND (unsatur\*[tiab] OR monounsatur\*[tiab] OR mono-unsatur\*[tiab] OR polyunsatur\*[tiab] OR polyunsatur\*[tiab] )) OR fish oils[mh] OR fish oil\*[tiab] OR plant oils[mh] OR plant oil\*[tiab] OR vegetable oil\*[tiab] OR n-3 oil\*[tiab] OR n3 oil\*[tiab] OR n3 fat\*[tiab]

**#2** - "Pregnancy"[Mesh] OR "Pregnancy Complications"[Mesh] OR "Maternal Exposure"[Mesh] OR "pregnant women"[Mesh] OR pregnan\*[tiab] OR pre-pregnancy[tiab] OR prenatal[tiab] OR pre-natal[tiab] OR maternal[tiab] OR mother\*[tiab] OR "Mothers"[Mesh] OR perinatal[tiab] OR peri-natal[tiab] OR pre-conception[tiab] OR preconception[tiab] OR peri-conception[tiab] OR periconception[tiab] OR "Peripartum Period"[Mesh] OR peripartum[tiab] OR peri-partum[tiab] OR gestat\*[tiab] OR natal[tiab] OR antenatal[tiab] OR ante-natal[tiab] OR puerperium[tiab] OR "Maternal Nutritional Physiological Phenomena"[Mesh] OR "Postpartum Period"[Mesh] OR postpart\*[tiab] OR post-part\*[tiab] OR postnatal[tiab] OR post-natal[tiab] OR post-delivery[tiab] OR postdelivery[tiab] OR after birth[tiab] OR Lactation[Mesh] OR lactat\*[tiab] OR breast feeding[Mesh] OR breastfe\*[tiab] OR breast fe\*[tiab] OR Milk, Human [Mesh] OR breastmilk[tiab] OR "breast milk"[tiab] OR "human milk"[tiab] OR "maternal milk"[tiab] OR "nursing women"[tiab]

**#3** - "Mental Disorders"[Mesh] OR mental disorder\*[tiab] OR "Cognition"[Mesh] OR Neuropsychological Tests[MeSH] OR cogniti\*[tiab] OR metacogniti\*[tiab] OR neurocogniti\*[tiab] OR neurodevelop\*[tiab] OR neurolog\*[tiab] OR "Depression"[Mesh] OR depress\*[tiab] OR anxi\*[tiab] OR "Psychomotor Performance"[Mesh] OR psychomotor[tiab] OR motor skill\*[tiab] OR "Executive Function"[Mesh] OR executive function\*[tiab] OR attention deficit disorder\*[tiab] OR attention deficit hyperactivity disorder\*[tiab] OR ADHD[tiab] OR behavior disorder\*[tiab] OR behaviour disorder\*[tiab] OR behavioral disorder\*[tiab] OR behavioural disorder\*[tiab] OR developmental disorder\*[tiab] OR Autis\*[tiab] OR Asperger\*[tiab] OR language processing[tiab] OR language delay\*[tiab] OR "Child Development"[Mesh] OR child develop\*[tiab] OR developmental delay[tiab] OR developmental disabilit\*[tiab] OR "Problem Solving"[Mesh] OR problem solv\*[tiab] OR developmental domain\* OR academic[tiab] OR "Academic Performance"[Mesh]

**#4** - #1 AND #2 AND #3

**#5** - #4 NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (editorial[ptyp] OR comment[ptyp] OR news[ptyp] OR letter[ptyp] OR review[ptyp] OR systematic review[ptyp] OR systematic review[ti] OR meta-analysis[ptyp] OR meta-analysis[ti] OR meta-analyses[ti] OR retracted publication[ptyp] OR retraction of publication[ptyp] OR retraction of publication[tiab] OR retraction notice[ti])

Filters: Publication date from 1980/01/01 to 2020/02/05; English

## Cochrane Central Register of Controlled Trials (CENTRAL)

- Provider: John Wiley & Sons
- Date(s) Searched: February 5, 2020
- Date range searched: January 1, 1980 – February 5, 2020
- Search Terms:

**#1** - "linolenic acid\*" OR "omega 3" OR "omega-3" OR "N3 fatty acid\*" OR "n-3 fat\*" OR pufa\* OR "alpha-linolenic acid\*" OR "eicosapentaenoic acid\*" OR "docosahexaenoic acid\*" OR [mh "Fatty Acids, Unsaturated"] OR ((fat OR fatty OR fats) NEAR/5 (unsatur\* OR monounsatur\* OR mono-unsatur\* OR polyunsatur\* OR poly-unsatur\* OR "linolenic acid\*")) OR [mh "fish oils"] OR fish oil\* OR [mh "plant oils"] OR "plant oil\*" OR "vegetable oil\*" OR "n-3 oil\*" OR "n3 oil\*" OR "n3 fat\*"

**#2** - [mh "Pregnancy"] OR [mh "Pregnancy Complications"] OR [mh "Prenatal Exposure Delayed Effects"] OR [mh "Maternal Exposure"] OR [mh "Pregnant Women"] OR [mh "Mothers"] OR [mh "Peripartum Period"] OR [mh "Maternal Nutritional Physiological Phenomena"] OR [mh "Postpartum Period"] OR pregnancy OR pre-pregnancy OR prenatal OR pre-natal OR maternal OR mother\* OR postpartum OR perinatal OR peri-natal OR pre-conception OR preconception OR peri-conception OR periconception OR peripartum OR peri-partum OR gestat\* OR natal OR antenatal OR ante-natal OR puerperium OR postpartum OR post-partum OR perinatal OR peri-natal OR puerperium OR postpartal OR post-partal OR postnatal OR "post delivery" OR "after birth" OR [mh Lactation] OR [mh "Breast Feeding"] OR [mh "Milk, Human"] OR lact\* OR breastfeeding OR breast-feeding OR breast feed\* OR breast-feed\* OR breastfed OR breast-fed OR breastfeed OR "human milk" OR "nursing women"

**#3** - [mh "Mental Disorders"] OR [mh "Cognition"] OR [mh "Cognitive Dysfunction"] OR [mh "Depressive Disorder"] OR [mh "Depression"] OR [mh "Psychomotor Performance"] OR [mh "Executive Function"] OR [mh "Attention Deficit and Disruptive Behavior Disorders"] OR [mh "Child Behavior Disorders"] OR "behavior disorder\*" OR "behaviour disorder\*" OR "behavioral disorder\*" OR "behavioural disorder\*" OR "developmental disorder\*" OR [mh "Child Development"] OR [mh "Autism Spectrum Disorder"] OR [mh "Developmental Disabilities"] OR [mh "Motor Skills Disorders"] OR [mh "Problem Solving"] OR "mental disorder\*" OR cognition OR cognitive OR metacognition OR neurocognitive OR neurodevelop\* OR depression OR anxiety OR "motor skill\*" OR "executive function\*" OR "attention deficit disorder\*" OR ADHD OR "developmental disorder\*" OR autism OR autistic OR Asperger\* OR "language processing" OR "language delay" OR "child develop\*" OR "developmental delay" OR "developmental disabilit\*" OR "motor skill\*" OR "developmental domain\*" OR "academic performance" OR [mh "academic performance"] OR "academic achievement" OR "academic failure" OR "academic success\*"

**#4** - #1 AND #2 AND #3

Filters – Date limited from 1980 to 2020, Trials

## Embase

- Provider: Elsevier
- Date(s) Searched: February 5, 2020
- Date range searched: January 1, 1980 – February 5, 2020
- Search Terms:

**#1** - 'Omega 3 fatty acid'/exp OR 'linolenic acid\*':ab,ti OR 'omega-3':ab,ti OR 'n-3 fatty acid\*':ab,ti

OR pufa\*:ab,ti OR 'alpha-linolenic acid\*':ab,ti OR 'eicosapentaenoic acid\*':ab,ti OR 'docosahexaenoic acid\*':ab,ti OR monounsatur\*:ti,ab OR mono-unsat\*:ti,ab OR polyunsat\*:ti,ab OR 'fish oils'/exp OR fish oil\*:ti,ab OR 'plant oils'/exp OR 'plant oil\*':ti,ab OR 'vegetable oil\*':ti,ab OR 'n-3 oil\*':ti,ab OR 'n3 oil\*':ti,ab OR 'n3 fat\*':ti,ab

**#2** - pregnancy:ab,ti OR 'pre pregnancy':ab,ti OR prenatal:ab,ti OR 'pre natal':ab,ti OR maternal:ab,ti OR mother:ab,ti OR mothers:ab,ti OR 'pre conception':ab,ti OR preconception:ab,ti OR 'peri conception':ab,ti OR periconception:ab,ti OR peripartum:ab,ti OR 'peri partum':ab,ti OR gestation\*:ab,ti OR natal:ab,ti OR antenatal:ab,ti OR 'ante natal':ab,ti OR postpartum:ab,ti OR post-partum:ab,ti OR perinatal:ab,ti OR 'peri natal':ab,ti OR puerperium:ab,ti OR postpartal:ab,ti OR post-partal:ab,ti OR postnatal:ab,ti OR 'post delivery':ab,ti OR 'after birth':ab,ti OR 'pregnancy'/exp OR 'pregnancy complication'/exp OR 'prenatal exposure'/exp OR 'maternal exposure'/exp OR 'pregnant woman'/exp OR 'mother'/mj OR 'puerperium'/exp OR 'maternal nutrition'/exp OR Lact\*:ab,ti OR breastfeeding:ab,ti OR breast-feeding:ab,ti OR 'breast feed\*':ab,ti OR breastfed:ab,ti OR 'breast fed':ab,ti OR breastfeed:ab,ti OR 'human milk':ab,ti OR 'nursing women':ab,ti OR 'lactation'/exp OR 'breast feeding'/exp OR 'breast milk'/exp

**#3** - 'mental disease'/exp OR 'cognition'/exp OR 'cognitive defect'/exp OR 'depression'/exp OR 'psychomotor performance'/de OR 'executive function'/de OR 'attention deficit disorder'/de OR 'autism'/exp OR 'child development'/de OR 'developmental disorder'/exp OR 'psychomotor disorder'/de OR 'problem solving'/de OR 'academic performance'/exp OR 'mental disorder\*':ab,ti OR cognition:ab,ti OR cognitive:ab,ti OR metacognition:ab,ti OR neurocognitive:ab,ti OR neurodevelop\*:ab,ti OR neurological:ab,ti OR depression:ab,ti OR anxiety:ab,ti OR 'executive function\*':ab,ti OR 'attention deficit disorder\*':ab,ti OR adhd:ab,ti OR 'developmental disorder\*':ab,ti OR autism:ab,ti OR asperger:ab,ti OR 'language processing':ab,ti OR 'language delay':ab,ti OR 'developmental delay':ab,ti OR 'developmental disabilit\*':ab,ti OR 'motor skill\*':ab,ti OR 'developmental domain\*':ab,ti OR 'academic performance':ab,ti OR 'academic achievement':ab,ti OR 'academic failure':ab,ti OR 'academic success\*':ab,ti

**#4** - #1 AND #2 AND #3

**#5** - #4 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND [english]/lim AND [1980-2020]/py NOT ([conference abstract]/lim OR [conference paper]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [systematic review]/lim OR [meta analysis]/lim)

## **Cumulative Index of Nursing and Allied Health Literature (CINAHL Plus)**

- Provider: EBSCOhost
- Date(s) Searched: February 5, 2020
- Date range searched: January 1, 1980 – February 5, 2020
- Search Terms:

**#1** - "omega-3" OR "omega 3" OR "N-3 fat\*" OR PUFA\* OR "alpha-linolenic acid\*" OR "eicosapentaenoic acid\*" OR "docosahexaenoic acid\*" OR "linolenic acid\*" OR (MH "fish oils) OR fish oil\* OR (MH "plant oils") OR "plant oil\*" OR "vegetable oil\*" OR "n-3 oil\*" OR "n3 oil\*" OR "n3 fat\*" OR (MH "Docosahexaenoic Acids") OR (MH "Eicosapentaenoic Acid")

**#2** - postpartum OR post-partum OR MH "Postpartum Period" OR postpartal OR post-partal OR postnatal OR post-natal OR "post deliver\*" OR "after birth" OR MH "pregnancy" OR MH "pregnancy complications" OR MH "Prenatal Exposure Delayed Effects" OR MH "Maternal

Exposure" OR MH "pregnant women" OR pregnan\* OR pre-pregnancy OR prepregnancy OR prenatal OR antenatal OR maternal OR mother OR mothers OR perinatal OR peri-natal OR periconception OR periconception OR MH "Peripartum Period" OR peripartum OR peri-partum OR gestation\* OR natal OR puerperium OR MH "Maternal Nutritional Physiological Phenomena" OR MH "Breast Feeding" OR breastfeeding OR breast-feeding OR MH "Milk, Human" OR "human milk" OR MH Lactation OR lactation OR lactating OR breastfeeding OR "breast feed\*" OR breast-feed\* OR breastfed OR breast-fed OR breastfeed\* OR "nursing women" OR "nursing mother\*"

**#3** - (MH "Mental Disorders+") OR "mental disorder\*" OR (MH "Cognition+") OR cognition OR cognitive OR metacognition OR neurocognitive OR neurodevelop\* OR neurological OR "cognitive dysfunction" OR "depressive disorders OR (MH "Depression") OR depression OR (MH "Anxiety") OR anxiety OR (MH "Psychomotor Performance") OR motor skill\* OR (MH "Executive Function") OR executive function\* OR (MH "Attention Deficit Hyperactivity Disorder") OR attention deficit disorder\* OR ADHD OR (MH "Child Behavior Disorders") OR (MH "Child Development") OR "child develop\*" OR developmental disorder\* OR (MH "Autistic Disorder") OR autism OR Asperger OR "language processing" OR language delay\* OR (MH "Developmental Disabilities") OR developmental delay\* OR developmental disabilit\* OR (MH "Motor Skills Disorders") OR motor skill\* OR (MH "Problem Solving") OR "problem solv\*" OR developmental domain\* OR (MH "academic performance") OR "academic performance" OR "academic achievement" OR "academic failure" OR academic success\*

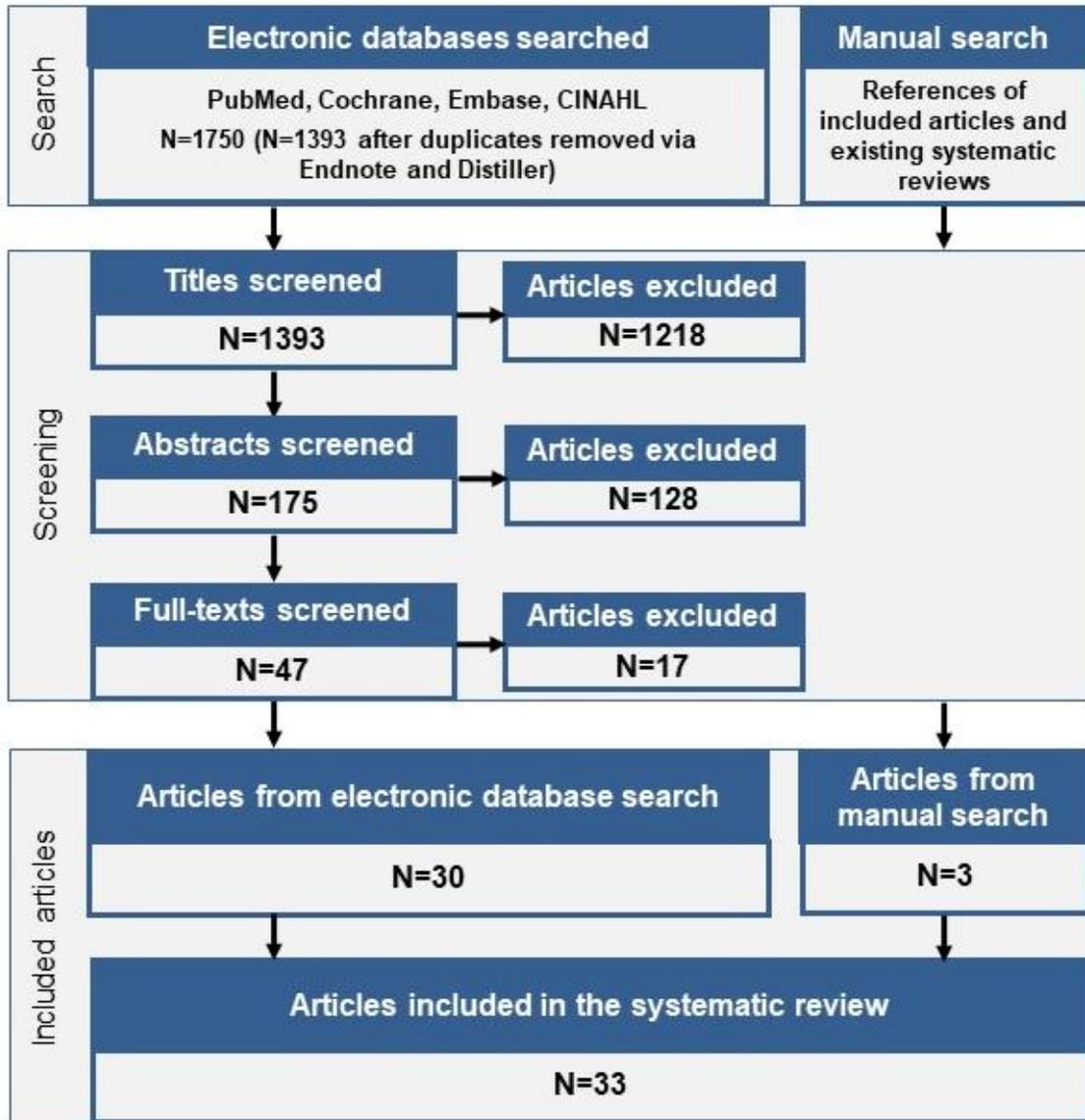
**#4** - #1 AND #2 AND #3

**#5** - NOT (MH "Literature Review" OR MH "Meta-Analysis" OR MH "Systematic Review" OR MH "News" OR MH "Retracted Publication" OR MH "Retraction of Publication) Filters - Published Date: 1980-2020, English Language; Human

## LITERATURE SEARCH AND SCREENING RESULTS

The flow chart (**Figure 2**) below illustrates the literature search and screening results for articles examining the systematic review question. The results of the electronic database searches, after removal of duplicates, were screened independently by two NESR analysts using a step-wise process by reviewing titles, abstracts, and full-texts to determine which articles met the inclusion criteria. Refer to **Table 11** for the rationale for exclusion for each excluded full-text article. A manual search was done to find articles that were not identified when searching the electronic databases; all manually identified articles are also screened to determine whether they meet criteria for inclusion.

**Figure 2: Flow chart of literature search and screening results**



## Excluded articles

The table below lists the articles excluded after full-text screening, and includes the categories of inclusion and exclusion criteria (see **Table 10**) that studies were excluded based on. At least one reason for exclusion is provided for each article, though this may not reflect all possible reasons for exclusion. Information about articles excluded after title and abstract screening is available upon request.

**Table 11. Articles excluded after full text screening with rationale for exclusion**

	Citation	Rationale
1.	Bernard, JY, De Agostini, M, Forhan, A, de Lauzon-Guillain, B, Charles, MA, Heude, B. The dietary n6:n3 fatty acid ratio during pregnancy is inversely associated with child neurodevelopment in the EDEN mother-child cohort. <i>J Nutr.</i> 2013. 143:1481-8. doi:10.3945/jn.113.178640 .	Intervention/Exposure
2.	Campoy, C, Escolano-Margarit, MV, Ramos, R, Parrilla-Roure, M, Csábi, G, Beyer, J, Ramirez-Tortosa, MC, Molloy, AM, Decsi, T, Koletzko, BV. Effects of prenatal fish-oil and 5-methyltetrahydrofolate supplementation on cognitive development of children at 6.5 y of age 1-5. <i>American Journal of Clinical Nutrition.</i> 2011. 94:1880S-1888S. doi:10.3945/ajcn.110.001107 .	Duplicate
3.	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. <i>Lipids.</i> 2011. 46:637-45. doi:10.1007/s11745-011-3557-x .	Intervention/Exposure
4.	Gould, JF, Treyvaud, K, Yelland, LN, Anderson, PJ, Smithers, LG, Gibson, RA, McPhee, AJ, Makrides, M. Does n-3 LCPUFA supplementation during pregnancy increase the IQ of children at school age? Follow-up of a randomised controlled trial. <i>BMJ Open.</i> 2016. 6:e011465. doi:10.1136/bmjopen-2016-011465 .	Protocol
5.	Hurtado, JA, Iznaola, C, Pena, M, Ruiz, J, Pena-Quintana, L, Kajarabille, N, Rodriguez-Santana, Y, Sanjurjo, P, Aldamiz-Echevarria, L, Ochoa, J, Lara-Villoslada, F. Effects of Maternal Omega-3 Supplementation on Fatty Acids and on Visual and Cognitive Development. <i>J Pediatr Gastroenterol Nutr.</i> 2015. 61:472-80. doi:10.1097/mpg.0000000000000864 .	Intervention/Exposure; Fortified food
6.	Jensen, CL, Voigt, RG, Prager, TC, Zou, YL, Fraley, JK, Rozelle, J, Turcich, M, Llorente, AM, Heird, WC. Effects of maternal docosahexaenoic acid (DHA) supplementation on visual function and neurodevelopment of breast-fed infants. <i>Pediatric research.</i> 2001. 49:448A.	Abstract
7.	Kim, Y, Ha, EH, Park, H, Ha, M, Kim, Y, Hong, YC, Lee, EJ, Kim, H, Chang, N, Kim, BN. Prenatal mercury exposure, fish intake and neurocognitive development during first three years of life: Prospective cohort mothers and Children's environmental health (MOCEH) study. <i>Sci Total Environ.</i> 2018. 615:1192-1198. doi:10.1016/j.scitotenv.2017.10.014 .	Intervention/Exposure

	Citation	Rationale
8.	Lauritzen, L, Jørgensen, MH, Mikkelsen, TB, Skovgaard, IM, Straarup, EM, Olsen, SF, Høy, CE, Michaelsen, KF. Maternal fish oil supplementation in lactation: Effect on visual acuity and n-3 fatty acid content of infant erythrocytes. <i>Lipids</i> . 2004. 39:195-206. doi:10.1007/s11745-004-1220-8 .	Intervention/Exposure; Fortified food
9.	Lauritzen, L, Jorgensen, MH, Olsen, SF, Straarup, EM, Michaelsen, KF. Maternal fish oil supplementation in lactation: effect on developmental outcome in breast-fed infants. <i>Reprod Nutr Dev</i> . 2005. 45:535-47. doi:10.1051/rnd:2005044 .	Intervention/Exposure; Fortified food
10.	Malin, AJ, Busgang, SA, Cantoral, AJ, Svensson, K, Orjuela, MA, Pantic, I, Schnaas, L, Oken, E, Baccarelli, AA, Tellez-Rojo, MM, Wright, RO, Gennings, C. Quality of Prenatal and Childhood Diet Predicts Neurodevelopmental Outcomes among Children in Mexico City. <i>Nutrients</i> . 2018. 10. doi:10.3390/nu10081093 .	Intervention/Exposure
11.	Miyake, Y, Tanaka, K, Okubo, H, Sasaki, S, Arakawa, M. Maternal fat intake during pregnancy and behavioral problems in 5-y-old Japanese children. <i>Nutrition</i> . 2018. 50:91-96. doi:10.1016/j.nut.2017.12.001 .	Intervention/Exposure
12.	Ogaz-Gonzalez, R, Merida-Ortega, A, Torres-Sanchez, L, Schnaas, L, Hernandez-Alcaraz, C, Cebrian, ME, Rothenberg, SJ, Garcia-Hernandez, RM, Lopez-Carrillo, L. Maternal dietary intake of polyunsaturated fatty acids modifies association between prenatal DDT exposure and child neurodevelopment: A cohort study. <i>Environ Pollut</i> . 2018. 238:698-705. doi:10.1016/j.envpol.2018.03.100 .	Intervention/Exposure
13.	Rees, A, Sirois, S, Wearden, A. Maternal docosahexaenoic acid intake levels during pregnancy and infant performance on a novel object search task at 22 months. <i>Child Dev</i> . 2014. 85:2131-9. doi:10.1111/cdev.12280 .	Intervention/Exposure
14.	Tofail, F, Kabir, I, Hamadani, JD, Chowdhury, F, Yesmin, S, Mehreen, F, Huda, SN. Supplementation of fish-oil and soy-oil during pregnancy and psychomotor development of infants. <i>J Health Popul Nutr</i> . 2006. 24:48-56.	Country
15.	Vollet, K, Ghassabian, A, Sundaram, R, Chahal, N, Yeung, EH. Prenatal fish oil supplementation and early childhood development in the Upstate KIDS Study. <i>J Dev Orig Health Dis</i> . 2017. 8:465-473. doi:10.1017/s2040174417000253 .	Supplementation during pregnancy assessed postpartum
16.	Waylen, A, Ford, T, Goodman, R, Samara, M, Wolke, D. Can early intake of dietary omega-3 predict childhood externalizing behaviour?. <i>Acta Paediatr</i> . 2009. 98:1805-8. doi:10.1111/j.1651-2227.2009.01434.x .	Intervention/Exposure
17.	Zeng, J, Yu, W, Dong, X, Zhao, S, Wang, Z, Liu, Y, Wong, MS, Wang, Y. A nanoencapsulation suspension biomimetic of milk structure for enhanced maternal and fetal absorptions of DHA to improve early brain development. <i>Nanomedicine</i> . 2019. 15:119-128. doi:10.1016/j.nano.2018.09.006 .	Human