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Omega-3 Fatty Acid Dietary Supplements Consumed During Pregnancy and Lactation and Child Neurodevelopment: A Systematic Review

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ABSTRACT

Background: Maternal nutrition during pregnancy and lactation has profound effects on the development and lifelong health of the child. Long-chain PUFAs are particularly important for myelination and the development of vision during the perinatal period.

Objectives: We conducted a systematic review to examine the relationship between supplementation with omega-3 fatty acids during pregnancy and/or lactation and neurodevelopment in children, to inform the *Scientific Report of the 2020 Dietary Guidelines Advisory Committee*.

Methods: We identified articles on omega-3 fatty acid supplementation in pregnant and lactating women that included measures of neurodevelopment in their children (0–18 y) by searching PubMed, CENTRAL, Embase, and CINAHL Plus. After dual screening articles for inclusion, we qualitatively synthesized and graded the strength of evidence using pre-established criteria for assessing risk of bias, consistency, directness, precision, and generalizability.

Results: We included 33 articles from 15 randomized controlled trials (RCTs) and 1 prospective cohort study. Of the 8 RCTs that delivered omega-3 fatty acid dietary supplements during pregnancy alone (200–2200 mg/d DHA and 0–1100 mg/d EPA for approximately 20 wk), 5 studies reported ≥1 finding that supplementation improved measures of cognitive development in the infant or child by 6%–11% ($P < 0.05$), but all 8 studies also reported ≥1 nonsignificant ($P > 0.05$) result. There was inconsistent or insufficient evidence for other outcomes (language, social-emotional, physical, motor, or visual development; academic performance; risks of attention deficit disorder, attention-deficit/hyperactivity disorder, autism spectrum disorder, anxiety, or depression) and for supplementation during lactation or both pregnancy and lactation. Populations with a lower socioeconomic status and adolescents were underrepresented and studies lacked racial and ethnic diversity.

Conclusions: Limited evidence suggests that omega-3 fatty acid supplementation during pregnancy may result in favorable cognitive development in the child. There was insufficient evidence to evaluate the effects of omega-3 fatty acid supplementation during pregnancy and/or lactation on other developmental outcomes. *J Nutr* 2021;151:3483–3494.

Keywords: pregnancy, lactation, cognition, attention deficit disorder, attention-deficit hyperactivity disorder, anxiety, depression, autism spectrum disorder, omega-3 fatty acids, systematic review

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Introduction

Maternal nutrition is a key factor influencing the health of both mothers and their children. The Developmental Origins of Health and Disease hypothesis posits that environmental exposures, including both under- and overnutrition, during early developmental stages increase the risk of developing metabolic and neurodegenerative disorders during later life (1, 2). Thus, a mother's health and nutritional status during the first 1000 days of a child's life, beginning at conception and continuing through the second year of life, may be exceptionally important to ensure optimal physical, social, and psychomotor growth and development and lifelong health (3). The intergenerational, or epigenetic, effects of intrauterine exposures (1) highlight the potential for long-term benefits of optimizing nutrition during pregnancy and lactation. Accordingly, understanding the relationship between consuming a healthy diet and preconception, pregnancy, and postpartum outcomes was the top-priority recommendation put forth by the Health in Preconception, Pregnancy, and Postpartum Global Alliance (4).

For the first time, the *Dietary Guidelines for Americans, 2020–2025* took a life course approach, including a new consideration of the first 1000 days of life (5). To support this new focus, the 2020 Dietary Guidelines Advisory Committee (hereafter referred to as the Committee) conducted systematic reviews, with support from the USDA's Nutrition Evidence Systematic Review (NESR) team, to examine the relationships between aspects of the maternal diet (including dietary supplements) consumed before and/or during pregnancy and lactation and child outcomes, including neurodevelopment.

Neurodevelopment, which begins at conception, is often described as a scaffolding process characterized by the rapid evolution of increasingly complex neurologic circuits. Thus, optimal growth and development in the first 1000 days demands that all obligatory components, including those provided by the diet, be available in sufficient quantities during critical periods of development (3). Both the timing and tempo of growth are important, as many aspects of development are sequential and cumulative (3, 6). Nutrients in commonly consumed foods that are particularly important during this early period of rapid development include protein, long-chain (LC) PUFAs, zinc, copper, iodine, iron, folate, and choline (7, 8). LC-PUFAs, produced endogenously or consumed from the diet, are essential for myelination and the development of vision during the perinatal period (3, 7–9). This systematic review of the literature examines the relationship between supplementation with omega-3 fatty acids during pregnancy and/or lactation and neurodevelopment in children.

Methods

This systematic review was conducted by the 2020 Committee, with support from the NESR team. NESR uses a rigorous, protocol-driven systematic review methodology designed to minimize bias, ensure the transparency and reproducibility of findings, and produce relevant, timely, and high-quality systematic reviews (10, 11). The full methods are detailed in the *Scientific Report of the 2020 Dietary Guidelines Advisory Committee* (12) and in the complete documentation of the Committee's systematic review (13), and are briefly described here.

The Committee developed a systematic review protocol that included an analytic framework (**Figure 1**), inclusion and exclusion criteria, and a literature search strategy. The analytic framework outlined core elements of the systematic review question (i.e., population; intervention or exposure and comparator; and outcomes) and included definitions for key terms, key confounders/covariates, and other factors to be considered when reviewing the evidence. The full protocol was originally published on dietaryguidelines.gov [now available from the 2020 Dietary Guidelines Advisory Committee, Nutrition Evidence Systematic Review Team (13)] and was available for public comment before screening began.

Inclusion and exclusion criteria

The authors defined the inclusion and exclusion criteria a priori, and a detailed list of these criteria was published (13). Studies of human participants from countries ranked as high or very high on the Human Development Index (14) that were available in English and published between 1 January 1980 and 5 February 2020 in peer-reviewed journals were eligible for inclusion in this systematic review. The following study designs were included: randomized controlled trials (RCTs), nonrandomized controlled trials, prospective and retrospective cohort studies, and nested case-control studies. Studies examining exposure to, including intake of, omega-3 fatty acids from dietary supplements (15), including multiple-nutrient supplements, were included if the comparator group(s) had different levels of exposure to omega-3 fatty acid supplements. Fortified foods were not considered in this review because their contribution to omega-3 fatty acid intake is generally low relative to the contribution from dietary supplements. Studies were excluded if supplementation of a nutrient other than omega-3 fatty acids varied between groups. The outcomes of interest included cognitive, language/communication, movement/physical, and social-emotional development; academic performance; attention deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD); anxiety; depression; and autism spectrum disorder (ASD).

With respect to the dietary exposures, women up to 6 mo before pregnancy and women who were pregnant or lactating were included. With respect to the outcomes, children (aged birth to 18 y) of participating mothers were included. Studies that only enrolled the following participants were excluded: women who became pregnant using Assisted Reproductive Technologies; women with multiple-gestation pregnancies (and studies that presented data for singleton and multiple-gestation pregnancies in aggregate); women who were diagnosed with a disease (other than obesity) or hospitalized for an illness or injury; and infants born before 37 wk of gestational age, with a birth weight less than 2500 g, or who were small for gestational age (i.e., birth weight less than the 10th percentile for the gestational age).

Literature search, screening, and selection

The NESR librarians conducted a literature search to identify all potentially relevant peer-reviewed articles in PubMed, CENTRAL,

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Supplemental Tables 1–9 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.
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Abbreviations used: ADD, attention deficit disorder; ADHD, attention-deficit hyperactivity disorder; ARA, arachidonic acid; ASD, autism spectrum disorder; BSID-II, Bayley Scales of Infant Development, second edition; DOMInO, DHA to Optimize Mother Infant Outcome trial; K-ABC, Kaufman Assessment Battery for Children; KUDOS, The Kansas University DHA Outcomes Study; LC-PUFA, long-chain PUFA; NESR, Nutrition Evidence Systematic Review; RCT, randomized controlled trial.

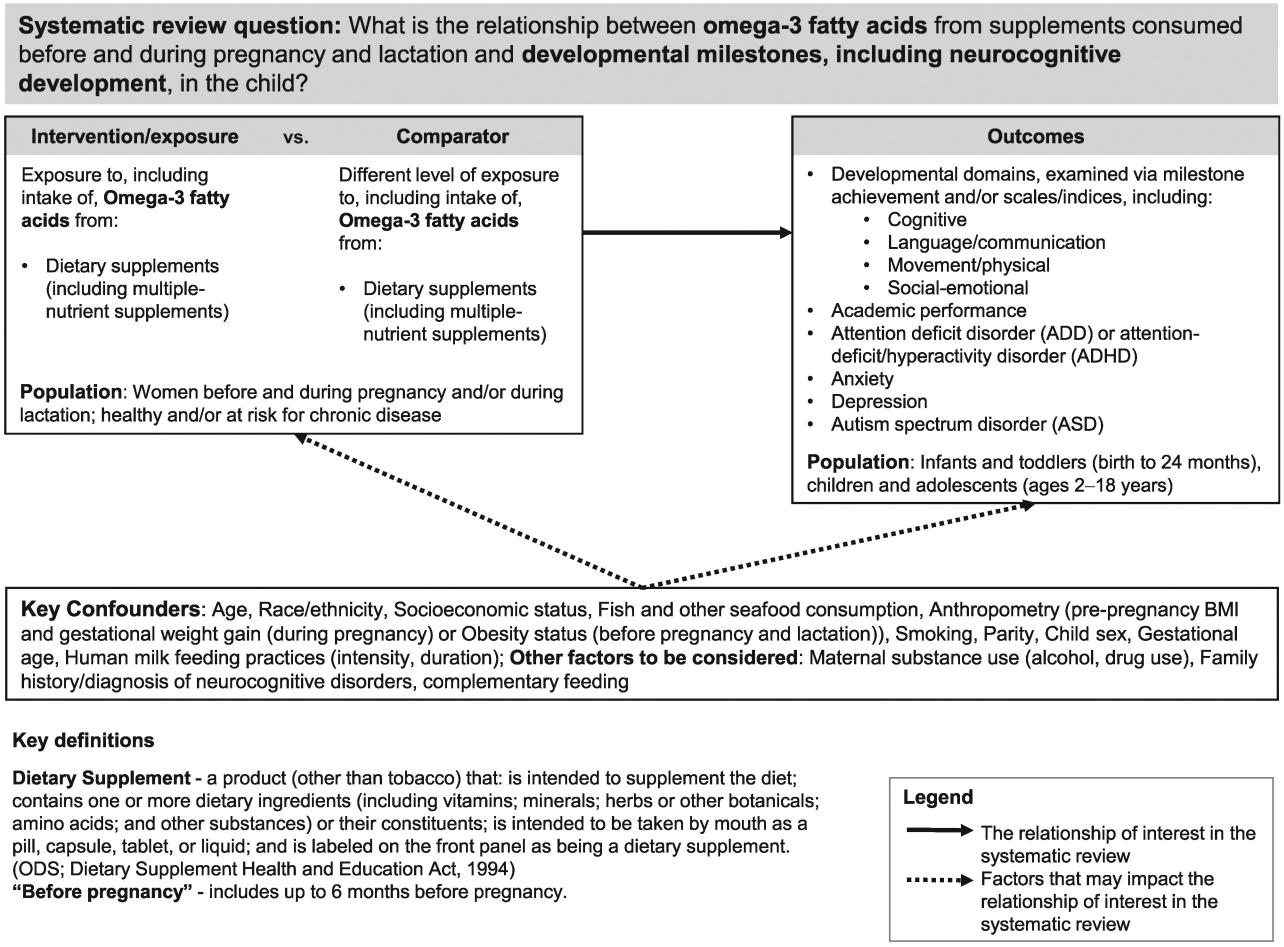

FIGURE 1 Analytic framework for the question related to the relationship between omega-3 fatty acid supplementation before and during pregnancy and/or lactation and neurodevelopment in the child.

Embase, and CINAHL Plus. The full search strategy was published a priori as part of the protocol (13). Two NESR analysts independently screened articles identified in the search by reviewing titles, abstracts, and full texts using a step-wise process to determine which articles met the inclusion criteria. NESR analysts also completed a manual search of the included articles' reference lists to find articles that were not identified in the original search. Next, NESR analysts extracted and summarized data from each included article to objectively describe the body of evidence. Finally, NESR analysts assessed the risk of bias for each article, using study design–specific tools developed to evaluate potential risks of bias in RCTs, nonrandomized trials, and observational studies (11, 16).

The Committee and NESR staff qualitatively synthesized the body of evidence and developed conclusion statements that answered the systematic review question. Next, the Committee graded the strength of evidence (i.e., strong, moderate, limited, or grade not assignable) underlying each conclusion statement using preestablished criteria for assessing the risk of bias, consistency, directness, precision, and generalizability (12). Finally, the Committee identified recommendations for future research to further address the research question.

Results

The literature search resulted in 1393 articles, after duplicates were removed. After screening titles, abstracts, and full texts, analysts identified 30 relevant articles; an additional 3 articles were identified via a manual search, for a total of 33 included articles from 15 RCTs (17–48) and 1 prospective cohort study (49). **Figure 2** presents details of articles excluded at each stage and **Supplemental Table 1** lists the articles excluded after full-text screening, with reasons for exclusion. **Table 1** summarizes the included articles and **Supplemental Tables 2** and **3** show results of the risk of bias assessments for the RCTs and prospective cohort study, respectively. Further information and results for each included study are detailed in **Supplemental Tables 4–9** and on the NESR website (13).

Population

The sample sizes of the RCTs ranged from 44 (28) to 900 (46) participants, and the prospective cohort study (49) included 258 participants. The studies were conducted predominantly in adult women (mean age ~26–34 y), and all had singleton pregnancies. Eight (17–20, 24–27, 29–31, 36–38, 42–48) of the 16 studies did not report participant race or ethnicity, 6 studies reported that the majority (55% to 100%) of participants were white (19, 23, 29, 32, 34, 40, 41, 49), 3 studies reported that 16% to 100% of participants were black (21, 22, 28, 35), and 3 studies reported that 6% to 13% of participants were Hispanic (21, 22, 28, 34). Five (21, 22, 28, 33–35, 49) of the 16 studies were conducted in the United States. In addition, 2 studies each were conducted in Australia (23, 25–27, 36, 37, 39, 45), Canada (32, 40, 41), and Germany (17, 20, 24), and 1 study each was conducted in Hungary (18, 19, 24), Iran (42),

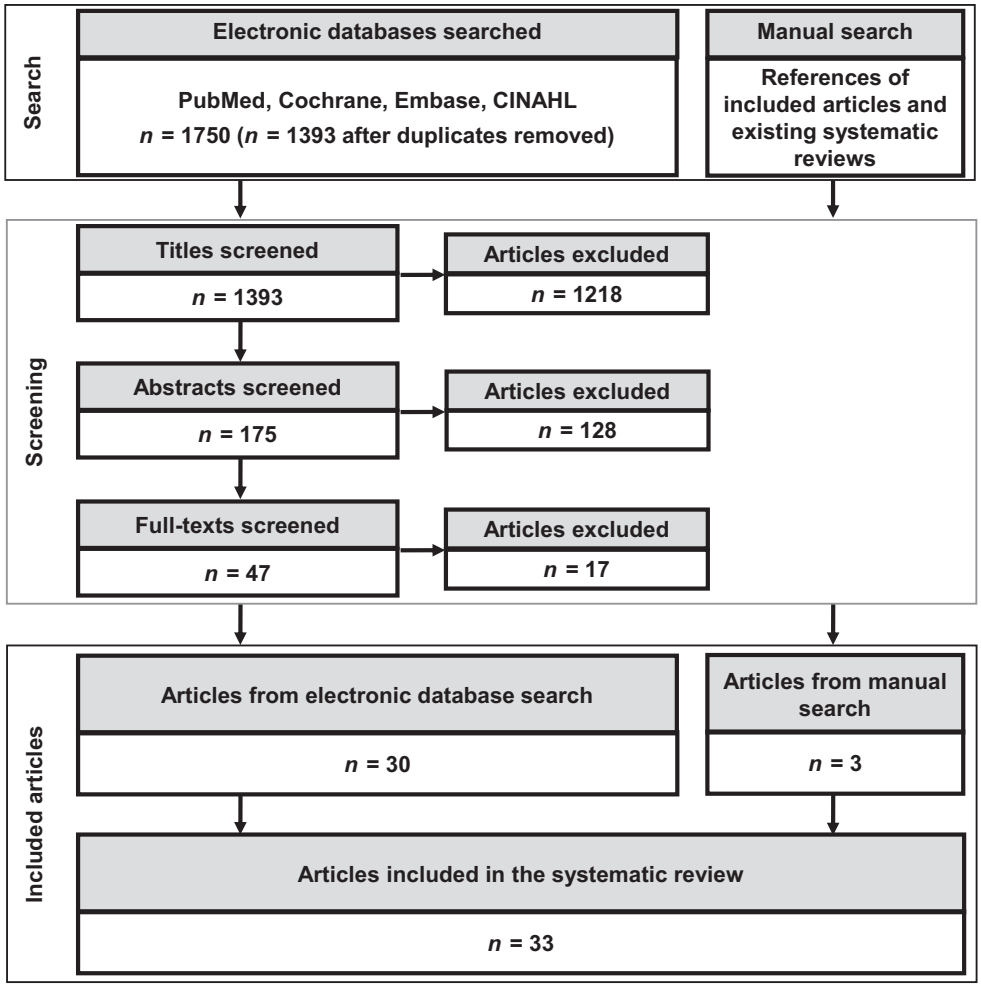

FIGURE 2. Flowchart of literature and screening results.

Mexico (43, 44, 46), the Netherlands (47, 48), Norway (29–31), Spain (18–20, 24), and the United Kingdom (38).

A majority of the studies reported that the participants, on average, had at least some college education (17, 21–23, 25–34, 36, 37, 39–41, 43–49). Two studies included predominantly (21, 22) or exclusively (35) women with low or middle incomes and 2 studies (19, 32) reported that >75% of participants had middle or high incomes. In 1 study, nearly 20% of participants reported insufficient income. The remaining studies did not report maternal or familial incomes.

Intervention/exposure

The body of evidence (Table 1) included studies that assessed interventions/exposures during pregnancy alone (11 RCTs and the 1 prospective cohort study) (18–28, 32, 35–49), during both pregnancy and lactation (3 RCTs) (17, 29–31, 47, 48), and during lactation alone (1 RCT) (33, 34). Seven RCTs provided DHA (21, 22, 28, 32–34, 38, 40, 41, 43, 44, 46), 4 RCTs provided both DHA and EPA (17–20, 23–27, 35–37, 39, 42, 45), and 1 RCT (47, 48) was a 2×2 trial of DHA and arachidonic acid (ARA). Helland et al. (29–31) provided 10 mL/d of cod liver oil. DHA doses ranged from 120 mg/d to 2.2 g/d and EPA doses ranged from 100 mg/d to 1.1 g/d. Although the dose of supplementation varied widely across studies, the findings did not vary meaningfully by dose (see description of outcomes below).

Most of the RCTs included a placebo composed of corn oil (29–31), soybean oil (35, 47, 48), or both (21, 22, 28, 32–34, 40, 41, 43, 44, 46). Placebos in other studies varied in fatty acid composition and contained either sunflower oil alone (38) or in combination with rapeseed and palm oils (25–27, 36, 45), olive oil (23, 39), or liquid paraffin (42). One study's placebo contained only the vitamins and minerals also included in the intervention supplement, minus DHA, EPA, and 5-methyltetrahydrofolate (18–20). Brei et al.'s (17) study did not include a placebo. The prospective cohort study (49) examined the omega-3 fatty acid supplementation dose as a continuous variable, but did not specify the supplement composition.

Outcome

The number of studies assessing each outcome by timing of omega-3 fatty acid supplementation is summarized in **Table 2**.

Cognitive development

Of the 8 RCTs that delivered omega-3 fatty acid dietary supplements during pregnancy alone, 5 studies (11 articles) reported at least 1 statistically significant finding that supplementation had a beneficial effect on cognitive development in the infant or child, but all 8 studies also reported at least 1 nonsignificant ($P > 0.05$) result (Table 1) (21–23, 25–27, 36, 43). Of these 8 trials with cognitive development measures, 2 conducted assessments during infancy only, 1 at age 1 wk (28), and 1 at ages 4 and 6 mo (42). Thus, the results of those 2 trials could not

TABLE 1 Summary of evidence on relationship between maternal omega-3 fatty acid supplementation and child development

Exposure period & outcome	Pregnancy		Lactation			Cognitive, *n*		Language, *n*		Motor, *n*		Visual, *n*		Social-emotional, *n*	
Cohort/Article | Supplement type & dose, mg/d	2nd trimester	3rd trimester	0–3 postnatal mo	3–6 postnatal mo	Age[1]	Favors intervention or control[2]	Favors neither[2]	Favors intervention or control[2]	Favors neither[2]	Favors intervention or control[2]	Favors neither[2]	Favors intervention or control[2]	Favors neither[2]	Favors intervention or control[2]	Favors neither[2]
DOMInO | 800 DHA + 100 EPA															
Makrides et al., 2010 (36)	⟷				18 mo	+1	2	0	3	0	1	—	—	0	2
Smithers et al., 2011 (45)	⟷				4 mo	—	—	—	—	—	—	0	5	—	—
Gould et al., 2014 (26)	⟷				27 mo	+2	16	—	—	—	—	—	—	—	—
Makrides et al., 2014 (37)	⟷				4 y	−2	14	0	1	—	—	—	—	−2	5
Gould et al., 2017 (27)	⟷				7 y	+1, −3	13	0	1	—	—	—	—	−1	0
NUHEAL | 500 DHA + 150 EPA															
Escolano-Margarit et al., 2011 (24)	⟷				4, 5.5 y	—	—	—	—	0	5	—	—	—	—
Campoy et al., 2011 (18)	⟷				6.5 y	0	3	—	—	—	—	—	—	—	—
Catena et al., 2016 (20)	⟷				8.5 y	0	4	—	—	—	—	—	—	—	—
Catena et al., 2019 (19)	⟷				6.6 y	0	1	—	—	—	—	—	—	—	—
POSGRAD | 400 DHA															
Stein et al., 2012 (46)[3]	⟷				1, 3, 6 mo	0	6	—	—	—	—	0	4	—	—
Ramakrishnan et al., 2015 (44)	⟷				18 mo	0	2	—	—	0	2	—	—	0	2
Ramakrishnan et al., 2016 (43)	⟷				5 y	+1	18	0	2	0	1	—	—	0	19
Perth | 2200 DHA + 1100 EPA															
Dunstan et al., 2008 (23)	⟷				2.5 y	+1	6	0	1	—	—	—	—	0	3
Meldrum et al., 2015 (39)	⟷				12 y	0	7	0	1	—	—	—	—	0	8
KUDOS | 600 DHA															
Colombo et al., 2016 (21)	⟷				4, 6, 9 mo	+3	2	—	—	—	—	—	—	—	—
Colombo et al., 2019 (22)[4]	⟷				10, 18, 24, 30, 36, 42, 48, 60, 72 mo	+4	14	0	6	—	—	—	—	0	4
Vancouver1 | 400 DHA															
Mulder et al., 2014(41)[5]	⟷				2, 9, 12, 14, 18 mo	0	1	+5	2	0	2	+1	1	—	—
Mulder et al., 2018 (40)	⟷				5.75 y	0	9	0	1	—	—	—	—	—	—
Pittsburgh | 450 DHA + 90 EPA + 40 DPA + 40 ETA															
Keenan et al., 2016 (35)	⟷				3 mo	—	—	0	2	0	1	—	—	+1	0
Tabriz | 120 DHA + 180 EPA															
Ostadrahimi et al., 2018 (42)	⟷				4, 6 mo	0	3	+1	4	0	2	—	—	0	2
Vancouver2 | 400 DHA															
Innis and Friesen, 2008 (32)	⟷				60 d	—	—	—	—	—	—	+1	1	—	—
Glasgow | 200 DHA															
Malcolm et al., 2003 (38)	⟷				1–5 d, 10 wk, 6 mo	—	—	—	—	—	—	0	8	—	—

(*Continued*)

TABLE 1 (*Continued*)

Exposure period & outcome	Pregnancy		Lactation			Cognitive, *n*		Language, *n*		Motor, *n*		Visual, *n*		Social-emotional, *n*	
Cohort/Article | Supplement type & dose, mg/d	2nd trimester	3rd trimester	0–3 postnatal mo	3–6 postnatal mo	Age[1]	Favors intervention or control[2]	Favors neither[2]	Favors intervention or control[2]	Favors neither[2]	Favors intervention or control[2]	Favors neither[2]	Favors intervention or control[2]	Favors neither[2]	Favors intervention or control[2]	Favors neither[2]
Kansas City | 600 DHA															
Gustafson et al., 2013 (28)	←	→			1 wk	+1	3	—	—	+1	0	—	—	0	2
Oslo | 10 mL/d cod liver oil															
Helland, 2001 (29)		←	→		6, 9 mo	0	3	—	—	—	—	—	—	—	—
Helland, 2003 (31)		←	→		4 y	+1	3	—	—	—	—	—	—	—	—
Helland, 2008 (30)		←	→		7 y	0	4	—	—	—	—	—	—	—	—
Gronigen | 220 mg/d DHA + 220 ARA or 220 DHA															
van Goor et al., 2010 (47)		←	→		2, 12 wk	—	—	—	—	–2	2	—	—	—	—
van Goor et al., 2011 (48)		←	→		18 mo	0	1	—	—	0	6	—	—	—	—
INFAT | 1020 DHA + 180 EPA + 9 Vitamin E															
Brei et al., 2017 (17)		←	→		4, 5 y	0	2	+1	2	+1	5	—	—	0	2
Houston | 200 DHA															
Jensen et al., 2005 (34)[6]			←	→	4, 8, 12 mo, 2.5 y	0	2	0	1	+1	1	–2	3	—	—
Jensen et al., 2010 (33)			←	→	5 y	+1	6	0	1	0	5	0	6	—	—

ARA, arachidonic acid; DOMInO, DHA to Optimize Mother and Infant Outcomes; DPA, docospentaenoic acid; ETA, eicosatetranoic 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; NUHEAL, Nutraceuticals for a Healthier Life; POSGRAD, Prenatal Omega-3 Supplementation on Child Growth and Development.

[1] Age of the child at outcome assessment

[2] Favors intervention (+) or favors control (–) indicates the results were statistically significant ($P < 0.05$), and "favors neither" indicates no statistically significant differences between groups ($P > 0.05$). Details of the results, including the level of statistical significance, are reported in Supplemental Tables 4–9.

[3] Cognitive outcomes at 1 and 3 mo; visual outcomes at 3 and 6 mo.

[4] Language outcomes at 18, 36, 42, 48, and 60 mo; social-emotional outcomes at 36, 48, 60, and 72 mo.

[5] Cognitive outcomes at 9 and 18 mo; language outcomes at 9, 14, and 18 mo; motor outcomes at 18 mo; visual outcomes at 2 and 12 mo.

[6] Cognitive outcomes at 2.5 y; language and motor outcomes at 12 mo and 2.5 y; visual outcomes at 4 and 8 mo.

TABLE 2 Strength of available evidence for systematic review of the relationship between maternal omega-3 fatty acid supplementation by timing of exposure and child neurodevelopmental outcomes

Outcomes	Timing of intervention or exposures		
	Pregnancy only	Both pregnancy and lactation	Lactation only
Cognitive development	Limited, favorable (8 RCTs) (18, 20–23, 25–28, 36, 39–44, 46)	Insufficient (3 RCTs) (17, 29–31, 48)	Insufficient (1 RCT) (33, 34)
Language development	Insufficient (7 RCTs) (22, 23, 25–27, 35, 36, 39, 40, 42, 43)	Insufficient (1 RCT) (17)	Insufficient (1 RCT) (33, 34)
Social-emotional development	Insufficient (7 RCTs) (22, 23, 26–28, 35, 36, 39, 42–44)	No evidence	No evidence
Motor development	Insufficient (7 RCTs) (18, 28, 35, 36, 41–44)	Insufficient (2 RCTs) (17, 47, 48)	Insufficient (1 RCT) (33, 34)
Visual development	Insufficient (5 RCTs) (32, 38, 41, 45, 46)	No evidence	Insufficient (1 RCT) (33, 34)
Academic performance	Insufficient (1 RCT) (27)	No evidence	No evidence
Risk of ADD/ADHD	Insufficient (1 RCT) (26, 27)	No evidence	No evidence
Risk of ASD	Insufficient (1 RCT, 1 PCS) (26, 49)	No evidence	No evidence
Risk of anxiety or depression	No evidence	No evidence	No evidence

ADD, attention deficit disorder; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; PCS, prospective cohort study; RCT, randomized controlled trial.

be compared with results of the other 6 trials. Among the other 6 trials (18–22, 26, 27, 36, 37, 39–41, 43, 44, 46), the maximum age at follow-up ranged from 5 to 12 y. Thus, the developmental domains assessed varied widely, as did the measures used to evaluate child performance in each of those domains. The doses and contents of the supplements provided also varied; 3 trials (21–23, 26, 27, 36–38) included both DHA and EPA, with doses ranging from 500 to 2200 mg/d for DHA and from 100 to 1100 mg/d for EPA; and 3 trials (18–20, 40, 41, 43, 44, 46) used only DHA, with doses of 400 to 600 mg/d. Most of the interventions began at 18 to 22 wk of gestation and continued through delivery. The studies provided little information on the baseline omega-3 fatty acid status, though all but 1 trial (21, 22) excluded women taking DHA-containing supplements. One of these 6 trials excluded women consuming more than 2 fish meals per week at enrollment (Perth trial) (23, 39). Three trials indicated that women had a low DHA intake (43, 44, 46) or low DHA status at baseline [The DHA to Optimize Mother Infant Outcome (DOMInO) and The Kansas University DHA Outcomes Study (KUDOS) trials] (21, 22, 26, 27, 36, 37).

Of the 6 studies with follow-up beyond infancy, 4 identified at least 1 significant difference in outcomes in favor of the group whose mothers received omega-3 fatty acid supplements. In the DOMInO trial (detailed in Supplemental Table 4) (26, 27, 36), the outcomes favoring the intervention group included general cognitive development at 18 mo ($P = 0.007$); sustained attention, working memory, and inhibitory control ($P \leq 0.05$) at 27 mo; and the perceptual reasoning subscale ($P = 0.03$) of the Wechsler Abbreviated Scale of Intelligence at age 7 y. By contrast, children in the intervention group of the DOMInO trial scored lower ($P \leq 0.03$) than those in the control group for assessments of executive function at age 4 y (26, 27), although assessments were based on parental reports. No significant differences were found for the remainder of the cognitive development assessments in the DOMInO trial ($P > 0.05$). In 1 study conducted in Mexico (43, 44), children in the intervention group scored 6.5% to 11.3% better ($P < 0.0001$) on 1 of the cognitive subscales (omissions) on the Kiddie Continuous Performance Test at age 5 y, but did not differ in the overall score or the other 3 subscales, nor on other measures of general cognitive performance, at age 18 mo or 5 y. In the KUDOS trial (22), children in the intervention group scored higher on 1 of the tests of executive function at ages 24 mo and 30 mo [effect size (d): 0.063 to 0.340; $P < 0.05$], but otherwise did not differ on the other tests performed at any age. In another study in Australia (23), children in the intervention group scored 6% higher ($P = 0.02$) on eye-hand coordination at age 2.5 y, but not on the other subscales of the Griffiths Mental Development Scales; at age 12 y, no significant differences were seen in cognitive development ($P > 0.05$), though only 48 children remained in the study (39). In the other 2 trials (18–20, 40, 41), no significant differences in cognitive development between groups were detected at any age ($P > 0.05$; Table 1; Supplemental Table 4).

Three RCTs delivered omega-3 fatty acid supplements during both pregnancy and lactation (Table 1; Supplemental Table 4) (17, 29–31, 47, 48). Of those 3 RCTs, 1 study reported a statistically significant finding that supplementation benefitted cognitive development in the child [i.e., 4% higher score ($P = 0.049$) on the Mental Processing Composite of the Kaufman Assessment Battery for Children (K-ABC); Table 1] (31). All 3 studies reported at least 1 statistically nonsignificant ($P > 0.05$) result for cognitive development on the following assessments: parent-reported Child Development Inventory (17), Fagan Test of Infant Intelligence, multiple scales of the K-ABC (30, 31), and the Bayley Scales of Infant Development, second edition (BSID-II) (48).

One RCT (33, 34) delivered omega-3 fatty acid supplements during lactation alone and showed a benefit of supplementation on 1 measure of cognitive development in the child (sustained attention subtest of the Revised Leiter International Performance Scale, 11% higher; $P = 0.008$; Table 1; Supplemental Table 4). However, the study also reported statistically nonsignificant ($P > 0.05$) results for other measures of cognitive development, including the BSID-II, the Clinical Adaptive Test, the Revised Wechsler Primary and Preschool Scale of Intelligence, the K-ABC, and the Developmental Test of Visual-Motor Integration-III.

Language development

Of the 7 RCTs (22, 23, 26, 27, 35, 36, 39–43) that examined the effect of omega-3 fatty acid supplementation during pregnancy alone on language development at ages ranging from 3 mo to 12 y (Table 1; Supplemental Table 5), 2 studies found statistically significant, favorable effects ($P = 0.002$–0.03; detailed results in Supplemental Table 5) of supplementation on at least 1 measure of language development in the child, at age 4 mo (42) and ages 14 and 18 mo (41). In the former, Ostadrahimi et al. (42) found beneficial outcomes of maternal supplementation on a continuous measure of language development behaviors at 4 mo, but no effect on this continuous measure at 6 mo, nor any effect on the risk of subnormal

language development at either age. All 7 RCTs reported at least 1 nonsignificant ($P > 0.05$) result for language development.

One RCT examined the effects of omega-3 fatty acid supplementation during both pregnancy and lactation on language development in the child (17), and reported a statistically significant favorable effect for only a single measure of language development at age 5 y ($P = 0.043$), but no association with other measures from the same tool at ages 4 and 5 y (Table 1; Supplemental Table 5).

The RCT that provided omega-3 fatty acid supplementation during lactation alone reported no association with multiple measures of language development at ages 12 mo, 2.5 y, and 5 y (33, 34).

Motor development

Of the 7 RCTs that examined the effects of omega-3 fatty acid supplementation during pregnancy alone on motor development in the child (ages 1 wk to 5.5 y) (18, 28, 35, 36, 41–44), 6 found no effect (Table 1; Supplemental Table 6) (18, 35, 36, 41–44). Gustafson et al. (28) found statistically significant, favorable effects of supplementation on a single measure of motor function in the neonate (13% higher mean score; $P = 0.038$).

Both of the RCTs that examined the effects of omega-3 fatty acid supplementation on motor development during both pregnancy and lactation found both statistically significant and null effects (ages 2 wk to 5 y; Table 1; Supplemental Table 6) (17, 47, 48). Brei et al. (17) found that a single measure of motor development at 5 y was more favorable in the intervention group than in the control group ($P = 0.039$), but no other measures were statistically significantly different. At 2 and 12 wk of age, van Goor et al. (47) found that infants whose mothers consumed DHA (but not those who consumed DHA + ARA) had a greater risk of mildly abnormal general movements ($P \leq 0.021$) compared to infants whose mothers consumed a placebo. 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. Further, van Goor et al. (47, 48) reported no differences between groups in the neurological classification at 2 wk or neurological optimality score at 12 wk of age (47), nor in the Hempel Assessment or BSID-II Psychomotor Development Index at 18 mo of age (48).

A single RCT examined the effects of omega-3 fatty acid supplementation during lactation alone on motor development in the child (Table 1; Supplemental Table 6) (33, 34). The authors reported 8% higher mean scores ($P = 0.008$) on 1 measure of motor development among toddlers in the supplemented group at age ~2.5 y (33), and noted that scores in both groups were higher than those in other studies of similarly aged children. Additional results revealed no association of supplementation with other measures of motor development at ages 12 mo, 2.5 y, and 5 y (33, 34).

Visual development

All 5 RCTs examining the effects of omega-3 fatty acid supplementation during pregnancy alone on visual development in the child reported at least 1 nonsignificant result (ages 1 d to 12 mo; $P > 0.05$; Table 1; Supplemental Table 7) (32, 38, 41, 45, 46). Two RCTs found statistically significant, favorable effects ($P < 0.05$; details in Supplemental Table 7) of omega-3 fatty acid supplementation on 1 measure of visual acuity in the child at approximately age 2 mo (32, 41).

No studies examined the effects of omega-3 fatty acid supplementation during both pregnancy and lactation on visual development in the child. The RCT that supplemented mothers during lactation alone (Table 1; Supplemental Table 7) (33, 34) reported unfavorable results for a single, electrophysiological measure of visual acuity at ages 4 and 8 mo (15% lower mean response; $P < 0.03$) (33, 34), but no association with another electrophysiological measure at the same ages and no association with other measures of visual development at ages 4 mo, 8 mo, and 5 y.

Social-emotional development

Seven RCTs examined the effects of omega-3 fatty acid supplementation during pregnancy alone on social-emotional development in the child (ages 1 wk to 7 y) (22, 23, 27, 28, 35–37, 39, 42–44) and 2 found statistically significant effects (Table 1; Supplemental Table 8) (27, 35, 37). In 1 study, children of mothers in the supplemented group had higher ($P = 0.04$) total parent-reported scores for difficulties or hyperactivity on a measure of child behavior at 4 y, but supplementation had a null effect on other parameters measured with the same tool (37); at 7 y, using an age-appropriate version of the same tool, the total difficulties score indicated unfavorable ($P = 0.02$) outcomes for the supplemented group (27). Another study suggested that omega-3 fatty acid supplementation resulted in a more attenuated (beneficial; $P = 0.02$) stress response at 3 mo (35). The remaining studies did not report any statistically significant results (22, 23, 28, 39, 42–44).

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 ages 4 and 5 y (Table 1; Supplemental Table 8) (17). No studies examined the effects of omega-3 fatty acid supplementation during lactation alone on social-emotional development in the child.

Other outcomes

One RCT (37) and 1 prospective cohort study (49) assessed ASD diagnoses, and both had null findings (Supplemental Table 9). Only 1 study examined academic performance, and it reported no effect of supplementation (27). The same study assessed hyperactivity disorders/ADHD, and reported no effect of supplementation at 4 y and a less favorable outcome, compared to the control group, at 7 y (27, 37). No evidence was available for the effects of omega-3 fatty acid supplementation on ADD, anxiety, or depression.

Risk of bias assessment

Overall, the RCTs included in this body of evidence had strong designs, were well conducted, and had few major flaws, resulting in an overall low risk of bias (Supplemental Table 2). The few concerns noted were unlikely to alter the conclusions and are described here. Two studies (29–31, 38) did not report details of randomization and allocation of the intervention, resulting in some concerns for risk of bias due to randomization. Additionally, deviations from the intended intervention in these 2 studies revealed a high risk of bias. Seven studies had possible or probable differences in proportions of and/or reasons for attrition between intervention and control groups, resulting in increased risk of bias due to missing outcome data (17, 21, 23, 25, 29–32, 35, 39). Two studies (17, 43) had high risk of bias due to outcome measurement for social-emotional development, because all results were based on parent reports of child behavior and could have been influenced by knowledge of

the intervention. Nearly all the included RCTs had some risk of bias due to selection of the reported results. Few studies published preregistered data analysis plans, and thus it was unclear whether the reported analyses were selected based on the findings. However, given that the reported domains were generally consistent with preregistered protocols and that all studies reported at least 1 nonstatistically significant ($P > 0.05$) result, the risk was judged to be moderate.

The single prospective cohort study in this review had a serious risk of bias due to confounding, classification of exposures, and the selection of reported results, and did not provide sufficient information to evaluate the risk of bias due to deviations from the intended exposures or missing data (Supplemental Table 3).

Conclusion statements

The strength of the evidence based on the above results is summarized in Table 2. A single conclusion statement received a grade of "limited" and suggested a favorable effect of omega-3 fatty acid supplementation during pregnancy on child cognitive development. Additional conclusions could not be drawn due to an insufficient number of studies for most intervention–outcome pairs, because of variation in outcome measures and results, and because most studies were conducted in samples with low sociodemographic diversity.

Discussion

This review evaluated the impacts of omega-3 fatty acid supplementation before and during pregnancy and lactation on developmental outcomes in the child. Based on the evidence from 8 RCTs (17 articles) published between 2006 and 2019, the Committee concluded that omega-3 fatty acid supplementation during pregnancy may result in favorable cognitive development in the child; however, this conclusion statement was graded as "limited."There was insufficient evidence to evaluate the effects of omega-3 fatty acid supplementation during pregnancy and/or lactation on language, social-emotional, movement/physical, motor, or visual development; academic performance; or risks of ADD, ADHD, ASD, anxiety, or depression.

Overall, the RCTs had low risk of bias regarding randomization, deviations from intended interventions, and outcome measurements. However, the results were equivocal both within and between studies, which could have been due to the wide variation in the timing of the outcome assessment. Thus, the ability to draw stronger conclusions was limited by the heterogeneity and inconsistencies of the findings. In addition, several studies did not provide evidence of a sufficient sample size to detect meaningful 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 longer-term outcome assessments. Lastly, the generalizability of this body of evidence to the United States was low because populations with lower socioeconomic statuses and adolescents were underrepresented and the studies lacked racial and ethnic diversity. The dose, duration, timing of intervention onset, and compliance with the protocols also varied.

Much less evidence was available for supplementation during lactation than during pregnancy. Given the mixed results, the small number of studies, relatively small sample sizes, risk of bias due to several study limitations, and inadequate information on the generalizability of results to the general US population, the evidence was insufficient to determine the relationship between omega-3 fatty acid supplementation during both pregnancy and lactation, or during lactation alone, and cognitive development in the child.

These conclusions are similar to those of a recent Cochrane review and meta-analysis (50), which stated that "very few differences between antenatal omega-3 LC-PUFA supplementation and no omega-3 were observed in cognition, IQ, vision, other neurodevelopment and growth outcomes, language, and behavior." A 2016 report by the Agency for Healthcare Research and Quality had similar findings (51). With regard to omega-3 fatty acid supplementation during lactation, a Cochrane systematic review and meta-analysis published in 2015 (52) stated "there is inconclusive evidence to support or refute the practice of giving LC-PUFA supplementation to breastfeeding mothers in order to improve neurodevelopment or visual acuity." A review in 2016 (53) came to a similar conclusion.

The importance of an adequate supply of omega-3 fatty acids for brain development in utero is not disputed (50, 54, 55). Both omega-3 and omega-6 fatty acids are involved in numerous processes for central nervous system development. Accumulation of DHA in the brain occurs rapidly during the second half of gestation and the first year after birth, suggesting that this is a critical period for an adequate supply from the diet, adipose stores, or synthesis from precursor fatty acids (e.g., alpha-linolenic acid) (56).

The effects of prenatal omega-3 fatty acid supplements on neurocognitive development of the child likely depend on the baseline omega-3 fatty acid adequacy of the mother's diet, as well as the ability of the child to produce LC-PUFA from their own precursor fatty acids in an amount sufficient to support optimal development of the central nervous system (56, 57). The studies in the present systematic review generally provided little information on the baseline omega-3 fatty acid status, but all but 1 (21, 22) of the trials of supplementation during pregnancy and cognitive development excluded women taking DHA-containing supplements before conception. Future research should consider dietary intake of omega-3 fatty acids from foods when assessing the effects of maternal omega-3 fatty acid supplementation on child development. The American Academy of Pediatrics (58) recommends that women who are breastfeeding consume 1 to 2 portions per week of fish/seafood high in DHA (200–300 mg/d on average) and EPA. The 2020 Committee report (12) found evidence that seafood intake during pregnancy is associated favorably with cognitive development in young children and may be associated favorably with language and communication development in children. Accordingly, the *Dietary Guidelines for Americans, 2020–2025* (5) recommends that women who are pregnant or lactating should consume at least 8 and up to 12 ounces of a variety of seafood per week (250-400 mg/d omega-3 fatty acids on average), from choices lower in methylmercury.

Future studies should also identify mothers who are most likely to benefit from supplementation by considering the potential modifying effects of the baseline maternal omega-3 fatty acid status and usual intakes in the study population. A review of NHANES data (1999 to 2014) showed that a majority of women in the United States who are pregnant (77%) or lactating (70%) use dietary supplements, compared to 45% of women who are not pregnant or lactating (59). However, these supplements may or may not include omega-3 fatty acids; 7.3% of women in the United States who are pregnant reported use of DHA/EPA dietary supplements

(60). In addition to diet, a woman's baseline status may be influenced by single nucleotide polymorphisms in the fatty acid desaturase gene cluster (61), which could alter preformed LC-PUFA requirements for pregnant women, as well as the amounts of LC-PUFA available to the fetus (62). Furthermore, the use of omega-3 fatty acid dietary supplements among infants and children has increased over time (63), which in general was not discussed within the body of literature we reviewed.

Additionally, further research is needed on whether the form and timing of supplementation with omega-3 fatty acids influence their effects on child development. While this review addressed the effects of omega-3 fatty acid supplements versus placebo, future studies should consider the effects of omega-3 fatty acids delivered within a multivitamin/mineral supplement, in fortified foods, and in foods naturally rich in omega-3 fatty acids, such as seafood. Furthermore, this review identified the paucity of evidence available to investigate the effects of supplementation during both pregnancy and lactation, and during lactation alone, on child development. Such research could better identify the potential 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. Importantly, future studies must strive to include a more diverse array of participants with regard to characteristics such as race, ethnicity, socioeconomic background, age, and usual diet. Finally, the bulk of the evidence in this review focused on the effects of omega-3 fatty acid supplementation on cognitive outcomes, and there is a dearth of research on the role of omega-3 fatty acid supplements in other child developmental outcomes, including language, motor, visual, and social-emotional development; academic performance; and risks of anxiety, depression, ADD/ADHD, and ASD.

In conclusion, supplementation with omega-3 fatty acids during pregnancy may be beneficial for cognitive development in children. However, the evidence reviewed was heterogeneous and did not provide clarity on the specific amounts of various omega-3 fatty acids that may be responsible for the benefits, if the relationship is indeed causal. Based on the evidence considered in this review, the 2020 Committee was unable to make a specific recommendation about routine supplementation with omega-3 fatty acids before and during pregnancy and lactation. More RCTs are needed that are adequately powered and that consider the maternal baseline status and genetic variation in fatty acid metabolism, along with consistent measurements of outcomes collected at multiple time points during child development.

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Data Availability

A registry for systematic reviews is available at dietaryguidelines.gov. Data described in the manuscript will be made publicly and freely available without restriction at https://nesr.usda.gov.

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