Analytic Review

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A Systematic Review of Omega-3 Fatty Acid Consumption and Cognitive Outcomes in Neurodevelopment

Abstract: *Introduction: This systematic review addresses the effects of* n-3 *long-chain polyunsaturated fatty acids consumption on human neurodevelopment. It evaluates articles published between 2000 and 2022 investigating the cognitive outcomes during the period of neurodevelopment: from fetal development to adolescence. For the purpose of this review the terms LC PUFA and omega-3 fatty acid will be used interchangeably. Method: Data were sourced from several major databases including PubMed (MEDLINE), Web of Science, and ProQuest Central. Randomized controlled trials (RCTs), nonrandomized controlled trials, prospective or retrospective cohort studies, and observational studies investigating the effects of omega-3 fatty acid consumption from dietary supplements, multiple-nutrient supplement, or food questionnaire on neurodevelopment were considered. Study population was separated in three developmental phases: (1) in-utero, (2) lactation/infancy, and (3) childhood/adolescence. Each article was evaluated for several key factors such as study type, type/dosage of PUFAs, number of subjects, length of intervention, participant age range, population characteristics, outcome measure (both primary/cognitive and secondary/other), results, conclusion, and confounding variables/limitations. Results: A total of 88 articles were included in the review, 69 RCTs and 19 longitudinal or observational studies. The results indicate equivocal effect of intervention, with some short-term benefits observed in the areas of visual attention, working memory, executive function, and communication. Omega-3 supplement might have a short-term positive impact on neurodevelopment in all three phases. Supplementation is recommended throughout life, rather than only during the earliest developmental stage.*

Keywords: omega-3s; LC PUFAs; cognition; neurodevelopment

> Although LC PUFAs supplied during infancy and *in-utero* seldom have shown significant cognitive effects, it appears that they do not persist at long-term follow-up assessments.

Introduction

As the most lipid-dense organ of the body, after adipose tissue, the brain requires fatty acids for purposes of fluidity, function, and structure.[1] Importantly, neither omega-3 (*n*-3) nor omega-6 (*n*-6) long-chain

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polyunsaturated fatty acids (LC PUFAs) can be synthesized *de novo* in human cells, meaning that dietary sources are important throughout life, particularly during several key, sensitive periods. Fatty acids affect white matter tracts in terms of myelination and fiber integrity, thereby influencing neural signaling.[2] Among LC PUFAs, docosahexaenoic acid, (DHA; 22:6, *n*-3) has received the most extensive attention throughout extant research, since it has the highest concentration in the brain; however, studies have also addressed eicosapentaenoic acid (EPA), alpha-linolenic acid (ALA), arachidonic acid (AA/ARA), and the importance of LC PUFA ratios. The frontal lobe, where complex cognitive processes occur, has a high concentration of DHA, which has a significant role in membrane fluidity and signal transmission.[3-5]

Westernization and the move toward diets with higher percentages of processed foods and lower consumption levels of dietary *n*-3 sources have led to concerns about population LC PUFA levels. Indeed, estimates of this shift suggest that traditional diets with 1:1 ratios of *n*-6 to *n*-3 PUFAs have been replaced by ratios closer to 20:1.[6]

Omega-3 Fatty Acid and *In-Utero* Cognitive Development

The prenatal period is the most frequently cited sensitive period during which *n*-3 LC-PUFAs are important to cognitive development. Based on epidemiological studies conducted in regions with high levels of fish intake, researchers identified a potential correlation between the maternal consumption of EPA and DHA and factors including gestational length and birth weight.[1]

During the third trimester an upsurge of PUFA accretion, primary DHA, in fetal brain matter occurs at a rate of 70 mg per day due to an increased cellular synthesis.[1,7] The accumulation of LC PUFAs is particularly important in the frontal lobe and hippocampus, areas associated with higher-order cognitive functioning.[8]

DHA supplementation has been previously related to extended gestational length, increased birth weight, and neurodevelopment.[9] Given that the third trimester is a significant period during which PUFAs are deposited in the fetal brain, many studies have attempted to identify deficiencies in or the effects of supplementation on preterm infants. Recently, the attention on the role of DHA in fetal development has been increased, and, in connection with concerns about consuming mercury-containing fish during pregnancy, the consumption of prenatal fish-oil and other *n*-3 supplements have increased.

Omega-3 Fatty Acid and Cognitive Development During Infancy. Supplementation with *n*-3 LC PUFAs during the infancy phase of development has its foundation in the longstanding research on the advantages of breastfeeding for cognitive development, and questions regarding whether this is due to the composition of human milk (including DHA), or other demographic factors associated with the decision to breastfeed.[10,11] Studies conducted during infancy have highlighted a positive correlation between PUFA supplementation and both cognitive and visual functions due to the PUFA accretion in fetal brain and retinal tissue, Supplementation studies during infancy have largely been focused on DHA, often in combination with EPA and AA, given their role in various neural processes including synapse maturation, processing speed, and the structure of the neuronal membrane.[3,11]

Omega-3 Fatty Acid and Cognitive Development During Childhood and Adolescence. While the third trimester of pregnancy and first 18 months of life are particularly significant phases of *n*-3 accretion in brain and retinal tissue, it is important to consider the continued process of cognitive development in early childhood and adolescence, and clarify the neurodevelopmental effects of LC PUFAs in this later phase. Researchers focusing on this age group are particularly driving attention to pathologies that affect cognitive development, including attention-deficit/hyperactivity disorder (ADHD), phenylketonuria, and autism spectrum disorder (ASD).

Review Objective. Omega-3 LC-PUFAs function as cell membrane components, tissue formation and neuroprotection has been largely proved.[12] However, omega-3 supplement effect on neurodevelopment addressed in a large number of studies and reviews have reported controversial conclusions. Therefore, the need of a comprehensive review to extrapolate and evaluate data from studies published in the last 2 decade.

In this review we summaries the finding on the effect of omega-3 supplementation on cognitive development across three neurodevelopmental periods: (1) *in-utero*, (2) lactation/infancy, and (3) childhood and adolescence. The objective is to evaluate the efficacy of omega-3 supplementation on neurodevelopment in different brain developmental phases from *in-utero* to adolescence.

Methodology

For the purposes of this comprehensive review, we searched PubMed (MEDLINE), Web of Science, and ProQuest Central, using filters for peer-reviewed articles published between 2000 and 2022. Search terms included: omega-3s; docosahexaenoic acid (DHA); cognitive function; macronutrients; healthy fats; polyunsaturated fatty acids; brain health; developmental outcomes; *n*-3 polyunsaturated fats;

LC PUFAs; dietary fats; and brain function.

Study Selection

Both the authors (DS and AS) were involved in the literature search, screening for eligible studies, and review. After articles were identified, the authors thoroughly reviewed titles, abstracts, and full texts, and selected the included ones according to the inclusion/exclusion criteria. Duplicate were eliminated. To confirm the comprehensiveness of the literature included, the Authors also consulted the reference lists of all articles published in the last 5 years, as well as previous literature review and meta-analysis articles, and used the "cited by" function in a university library database-wide search; additional abstracts were reviewed, and appropriated articles were included.

Inclusion and Exclusion Criteria

The authors defined inclusion and exclusion criteria a priori and included the following study designs: randomized controlled trials (RCTs), nonrandomized controlled trials, prospective or retrospective cohort studies, case-control studies, and observational studies. Only articles written in English published between 2000 and 2022 were included. Studies investigating the effects of omega-3 fatty acid intake from dietary supplements or multiple-nutrient supplement on cognition, or studies analyzing dietary omega-3 intake through a food questionnaire were considered. The populations included were: (i) *in-utero*, (ii) lactation/infancy, and (iii) childhood and adolescence. Case studies and studies in which PUFAs supplementation was not a primary (or differentiable) independent variable were not considered in this review.

Data Extraction

Included articles were analyzed and data were extracted using a custom data extraction form developed by DS and AS. The outcome of interests for the *in-utero* population were: communication and language, attention tasks, and visual development. For the lactation/infancy were: communication, intelligence, working memory, attention, and problem solving. For the childhood and adolescence population were: attention and executive functioning, information processing, speeds and impulsivity, memory, and cognitive pathologies.

After publication analysis, we extracted the following categories: study type, LC PUFA dosage and composition, sample number, length of intervention, subjects age, and population characteristics. Study characteristics and outcomes were also extrapolated. We reported: primary and secondary outcome (eg cognitive tests result, memory function, learning test), summary of result and conclusion, study limitation and funding sources.

Results

The literature search resulted in a total of 501 articles. Articles initially excluded were duplicates (n = 120), animal studies (n = 68), studies not focusing on omega-3 (88), studies with non-cognitive outcomes measure (n = 33). We reviewed the abstract of the remaining 181 articles and selected 81 pertaining to neurodevelopment to read in full. We narrowed these to a final set of 71 articles that met the inclusion criteria. To have a more comprehensive review, we expanded the search to the reference list of the included articles and reviewed an additional 34 abstracts of which 17 were included.

Of the 82 included articles, 26 investigated omega-3 prenatal supplementation (8 RCTs, 12 revision of RCTs, and 6 observational studies), 26 investigated omega-3 supplementation during infancy (19 RCT, 4 previous RCTs, and 3 observational studies), and 36 articles investigated omega-3 supplementation during childhood and adolescence (25 RCTs, 7 observational studies, and 4 secondary analyses of previous RCTs).

In-Utero Supplementation

To our knowledge, only two large scale ($N > 500$) studies have been conducted on humans to assess the cognitive outcomes of n-3 LC PUFA supplementation *in-utero*: the DOMInO trial,[13] and the POSTGRAD cohort study.[14] Study sample sizes for the remaining included publications ranged from 76 to 350.

The studies included in this review primarily assessed the effect of omega-3 DHA supplementation ($n = 9$). In the included studies DHA dosage levels ranged from 220 mg to 800 mg per day. Rees et al. also assessed for DHA levels, but via a food frequency questionnaire rather than a supplementation intervention.[15] In the remaining studies DHA was combined with EPA,[16-19] and AA.[20] In terms of intervention lengths, the studies reviewed here featured gestational supplementation ranging from week 12 to week 22 of gestation. The studies used a broad range of cognitive outcome measures, with the Kaufman Assessment Battery for Children (K-ABC) appearing most frequently.

Importantly, while most studies cited academic and/or governmental funding sources, industry interests also appeared as financial contributors to several of the studies: a company that produces omega-3 supplements[18,19,21]; a dairy industry stakeholder[20]; and a nutrition company.[15] Table 1 presents the study and population characteristics of the 26 studies included in this analysis of *in-utero* supplementation studies.[22-32] Table 2 provides the instrumentation, results, and

Table 1.

In-Utero Supplementation Studies: Study Types and Participant Characteristics.

	Study type	Type/dosage of PUFAs	*N*	Length of intervention	Participant age range	Population characteristics
Boucher et al. (2011)	Prospective, longitudinal	Fish eating community as setting; diet questionnaire	153	Non-intervention; 11-year follow-up	Mean = 11.3	School-age Inuit children from Nunavik
Brei et al. (2017)	Follow-up of RCT	1020 mg DHA+180 mg EPA+9 mg vitamin E	130	15 weeks' gestation through 4 months postpartum	*In-utero*/infancy at time of intervention; follow-up at 4-5 years	Healthy pregnant women
Campoy et al. (2011)	Follow-up study of the NUHEAL (Nutraceuticals for a Healthier Life) cohort	500 mg DHA and 150 mg of EPA per day; 5-methyltetrahydro-folate (5-MTHF); both; or a placebo during pregnancy; infants in the intervention group received formula with .5% DHA and .4% AA	270 in original study; 154 analyzed in follow-up	20 weeks' gestation through delivery; formula supplementation through 6 months	*In-utero*/infancy at time of intervention; follow-up at 6.5 years	Healthy pregnant women
Colombo et al. (2016)	RCT	600 mg DHA per day	350 randomized	Last two trimesters (14.5 weeks to delivery)	*In-utero* (follow-up at 4, 6, and 9 months)	n/s
Colombo et al. (2019)	RCT (follow-up)	600 mg DHA per day	78 in placebo and 83 in intervention completed 72-month follow-up	Last two trimesters (14.5 weeks to delivery)	10 month-72-month follow-up	n/s
Daniels et al. (2004)	Observational	Fish intake measured by questionnaire	7421	Prenatal; non-intervention	Cognitive testing at 15 and 18 months	n/s
Dijck-Brouwer et al. (2005)	Observational	Umbilical artery and vein FA concentrations	317	Prenatal; non-intervention	Testing day 10-14 after birth	Born at 37-42 weeks' gestation
Dunstan et al. (2008)	RCT	1.1 g EPA and 2.2 g DHA per day	98	20 weeks' gestation through delivery	*In-utero* (follow-up at 2.5 years)	n/s
Escolano-Margarit et al. (2011)	RCT	500 mg/d DHA +150 mg/d EPA), 400 mg/d 5-methyltetrahydrofolate, both, or placebo	157	20 weeks' gestation through delivery	*In-utero* (follow-up at 5.5 years)	Healthy pregnant women
Gould et al. (2014)	Secondary analysis of the DOMInO trial	800 mg DHA/day	185	20 weeks' gestation through delivery	*In-utero* (follow-up at 27 ± 2 months)	18-21 week-gestation singleton pregnancies; no fetal abnormalities
Gould et al. (2016)	Secondary analysis of the DOMInO trial	800 mg DHA/day	2399 randomized in original study; 646 in 4-year follow-up	20 weeks' gestation through delivery	*In-utero* (follow-ups at 18 months and 4 years)	18-21 week-gestation singleton pregnancies; no fetal abnormalities
Helland et al. (2001)	RCT	10 mL of cod liver oil (1183 mg of DHA, and 803 mg of EPA) per day	590 recruited; 341 mothers completed intervention; 245 infants complied with follow-up request	17-19 weeks' gestation to 3 months after delivery	*In-utero* (follow-up at 6 and 9 months)	Healthy pregnant women
Helland et al. (2003)	RCT (follow-up—subgroup analysis)	Human milk containing 270% more DHA and 88% less AA than that of control group mothers	76	18 weeks' gestation to 3 months after delivery	*In-utero* and during lactation (follow-up at 4 years)	Healthy pregnant women; infants who were breastfed at 3 months of age
Helland et al. (2008)	RCT (follow-up)	10 mL of cod liver oil (1183 mg of DHA, and 803 mg of EPA) per day	590 recruited [. . .] 84 tested for K-ABC at 4 years; 143 tested for K-ABV at 7 years	17-19 weeks' gestation to 3 months after delivery	*In-utero* (follow-up at 4 and 7 years)	Healthy pregnant women
			11 875			n/s

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Table 1. (continued)

Hibbeln et al. (2007)	Secondary analysis of Avon Longitudinal Study of Parents and Children	Food-frequency questionnaire		Non-intervention; seafood consumption at 32 weeks' gestation assessed	*In-utero*; children assessed at 6, 18, 30, 42, and 81 months	
Hurtado et al. (2015)	RCT	400 mg DHA/day	110	28th week of gestation and lactation period	*In-utero* and during lactation	Healthy; appropriate weight gain; no DHA supplementation during pregnancy
Makrides et al. (2010)	RCT (DOMInO trial)	800 mg DHA/day	2320 women evaluated for depressive symptoms; 694 children completed follow-up	20 weeks' gestation through delivery	*In-utero*; follow-up at 18 months	Singleton pregnancies; approached at > 21 weeks 'gestation
Mendez et al. (2009)	Prospective cohort	Seafood consumption during pregnancy assessed	392	Non-intervention; results stratified by breastfeeding duration	Neurodevelopment assessed at age 4	Full-term children; data on maternal diet during pregnancy
Mulder et al. (2018)	RCT (follow-up study)	800 mg DHA/day	98 in follow-up	16 weeks' gestation to delivery	*In-utero*; follow-up at 5-6 years	Follow-up only of singleton, term infants without neurological development affecting diseases
Oken et al. (2005)	Prospective cohort	Non-interventional; fish servings per week and hair mercury assessed	135	Non-intervention	*In-utero*; infants assessed at 6 months of age	Singleton pregnancy
Ostadrahimi et al. (2018)	RCT	120 mg DHA and 180 mg EPA per day	150	20 weeks' gestation to 30 days postpartum	*In-utero*; follow-up at 4 and 6 months of age	Low-risk singleton pregnancy; follow-up of infants without major congenital deformities or metabolic disorders
Ramakrishnan et al. (2016)	RCT (follow-up of findings from the POSTGRAD study)	400 mg DHA/day	10 494 pregnant women randomized; 797 children included in follow-up	18-22 weeks' gestation through delivery	*In-utero*; follow-up at 5 years	n/s
Rees et al. (2019)	Observational	Non-intervention (food frequency questionnaire to estimate DHA levels)	125	Second and third trimester DHA levels assessed	*In-utero*; follow-up at 4.5 and 9 months	Single, healthy pregnancy; no significant health problems
Steer et al. (2013)	Secondary analysis of Avon Longitudinal Study of Parents and Children cohort	Maternal FAs in erythrocytes	2839	Non-intervention	*In-utero*; follow-up at 8 years	Pregnant women in Bristol; per original study
van Goor et al. (2010)	RCT	220 mg per day of DHA, 220 mg of DHA and 220 mg AA per day, or a placebo	119	17 weeks' gestation through 20 weeks postpartum	*In-utero*; follow-up at 2 and 12 weeks postpartum	Healthy pregnant women
Vollet et al. (2007)	Secondary analysis of Upstate KIDS Study (birth cohort)	Non-intervention; self-reported consumption of fish oil before and during pregnancy	5845	Non-intervention	*In-utero*; children assessed from 4 months to 3 years of age	Mothers from the original study who had self-reported fish oil supplementation

limitations information for the included studies.

Overall, the extant RCTs and RCT follow-up studies that feature *in-utero n*-3 LC PUFA supplementation have yielded mixed results. The largest study to date, the DOMInO trial ($N = 2399$; follow-up with 726 children), found that DHA supplementation during pregnancy had no significant effect on either maternal depression levels 6 months postpartum or the children's mean cognitive composite or mean language composite scores on the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). Importantly, these null results are at odds with those of previous epidemiological studies, which the authors noted may have

Table 2.

In-Utero Supplementation Studies: Instrumentation, Results, and Limitations.

	Outcome measures		Results	Conclusion	Confounding variables/limitations	Funding source
	Primary/cognitive	Secondary/other measures				
Boucher et al. (2011)	Continuous visual recognition task	Digit span forward from Wechsler Intelligence Scales for Children, 4th edition; California Verbal Learning Test–Children's Version	Higher levels of cord DHA concentration correlated with improved memory performance at 11 years of age	Prenatal fish consumption improves cognitive outcomes in school age, regardless of seafood contaminant amounts	Non-RCT	NIH/National Institute of Environmental Health Sciences; Northern Contaminants Program, Indian and Northern Affairs, Canada; the NIH/ National Institute on Alcohol Abuse and Alcoholism; Joseph Young Sr Fund from the State of Michigan
Brei et al. (2017)	Child development inventory (CDI); assessment of mirror movements		No significant difference among groups on the CDI or in mirror movements	The results did not indicate either benefits or harms of a prenatal shift in *n*-3:*n*-6 ratio with supplementation	Small sample size; insufficient statistical power	Else Kroner-Fresenius Foundation, Bad Homburg; the European Union-funded Early Nutrition Programming Project consortium; German Ministry of Education and Research via the Competence Network Obesity
Campoy et al. (2011)	Kaufman Assessment Battery for Children (K-ABC)	FAs in maternal blood at 20 and 30 weeks; FAs in cord blood	No significant differences among the four intervention groups in K-ABC scores; however, higher DHA in maternal erythrocytes did correlate with a higher mental processing composite score	Further research required on efficacy of supplementation beyond early childhood and optimal doses at different developmental stages	High attrition; disparities in groups' representation of parental educational level and birth anthropometric measures	Commission of the European Community–specific Research and Technological Development Programme
Colombo et al. (2016)	Visual habituation (looks to habituation, look duration, sustained attention	Heart rate; task completion and fussiness	Prenatal DHA supplementation correlated with improved performance on attentional tasks during the first year of life	Results suggest attentional task benefits; further research required to determine whether prenatal supplementation benefits persist into early childhood	Failure to control for postnatal dietary DHA intake; exclusion of children born before 34 weeks' gestation	Eunice Kennedy Shriver National Institute of Child Health and Development, the Office of Dietary Supplements, and the Kansas Intellectual and Developmental

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						Disabilities Research Center
Colombo et al. (2019)	Cognitive and behavioral assessments	n/a	Maternal blood DHA during pregnancy correlated with higher verbal and full-scale IQ at 5-6 years, but this result disappeared after controlling for SES	No long-term positive effects of DHA supplementation	Both intervention and control groups may have achieved sufficient DHA levels; SES as a confounding factor	NIH
Daniels et al. (2004)	MacArthur Communicative Development Inventory; Denver Developmental Screening Test		Maternal prenatal fish intake and infant postnatal fish intake associated with higher development scores; threshold effect with more than 2 fish meals per week	While mercury levels increased with fish intake, these did not appear to affect development; pre- and postnatal fish consumption appears to have safe, cognitive benefits	Non-intervention; potential bias in food frequency questionnaires	Medical Research Council; Wellcome Trust; Department of Health, Department of the Environment, and DfEE; Nutricia; "other companies"
Dijck-Brouwer et al. (2005)	Neonatal neurological examination technique as described by Prechtl	Obstetrical history	Infants who were neurologically abnormal tended to have lower umbilical vein DHA levels	Low levels of DHA, AA, and EFA have a negative impact on neurological optimality among neonates	Results do not imply causation; further research required	Numico Research BV
Dunstan et al. (2008)	Griffiths Mental Development Scales (GMDS)	Cord blood FA levels	Hand-eye coordination scores significantly positively correlated with EPA level in cord blood at 36 months, and inversely correlated with AA level at birth	Consistent with other findings on the benefit of *n*-3 LC PUFAs for visual development; supplementation is safe and warrants further study	Small sample size; potential type 1 error due to multiple comparisons	Raine Medical Research Foundation of Western Australia and the National Health and Medical Research Foundation of Australia
Escolano-Margarit et al. (2011)	Touwen examination	Maternal and neonatal LC-PUFA levels in plasma and erythrocyte PL	Likelihood of high neurological optimality score increased with cord blood DHA level	While supplementation did not result in higher neurological examination scores, DHA in cord blood does correlate with better NOS scores long-term	High attrition; neurological assessment performed by different people	Commission of the European Communities
Gould et al. (2014)	Distraction; working memory and inhibitory control (WMIC)	n/a	Neither attention nor working memory/ inhibitory control measures differed between the intervention and control groups	Null findings consistent with other studies on well-nourished children born at term	Power to detect WMIC measure less than originally intended; larger sample may have changed result	University of Adelaide the National Health and Medical Research Council of Australia, and the NIH
Gould et al. (2016)	Bayley-III (cognitive composite and language composite scores), and differential ability scales (DAS)	Gestational age at birth, birth weight, birth length, and birth head circumference; maternal PPD; child allergic disease	Children in the supplementation scored higher on the Bayley-III, but only when their mothers had not completed further education;	The results indicate the importance of assessing subgroups of supplemented populations to identify potential moderating variables	Powered to detect supplementation in overall sample rather than subgroups	Australian National Health and Medical Research Council

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			smoking appeared to nullify benefits in the non-smoking group			
Helland, et al. (2001)	Novelty preference using the Fagan test	Gestational length and birth weight	Novelty preference test did not indicate any differences in cognitive function at either 6 or 9 months between the groups; high concentration of DHA in umbilical plasma did correlate with higher gestational age	Already high FA intake among population may have affected the results, and suggested conducting a similar study should be conducted with population with a low intake of DHA or among mothers who did not intend to breastfeed	May have been too early to determine a statistically significant difference in novelty preference; later/more subtle testing may be required	Peter Møller, Avd. Orkla ASA (omega-3 supplement industry) and “Aktieselskabet Freia Chocoladefabriks Medicinske Fond”
Helland et al. (2003)	K-ABC	Maternal dietary intake	Significantly higher scores on the mental processing composite of the K-ABC in children from the intervention group than those in the control group	Supplementation with LC PUFAs during pregnancy and lactation improves children’s intelligence at 4 years of age	Small subsample size	Peter Møller, avd. Orkla ASA (omega-3 supplement industry), Eckbos Legater, and Aktieselskabet Freia Chocolade-fabriks Medicinske Fond
Helland et al. (2008)	K-ABC	Body mass index	At 4 years of age, the cod liver oil group demonstrated higher scores; no significant difference at 7 years of age, excepting slightly higher scores for sequential processing in the intervention group, which was deemed insignificant	The positive effect of *n*-3 LC PUFA supplementation may be diluted by other factors like nutrients, drugs, social stimulation, and diseases by the age of 7	Methods of cognitive testing may not be sufficiently sensitive	Peter Möller Department of Orkla ASA (omega-3 supplement industry), Johan Throne-Holst Foundation for Nutrition Research, Freia Chocolade Fabriks Medicinske Fond, the Research Council of Norway, and the Thematic Program on Perinatal Nutrition, Faculty of Medicine, University of Oslo
Hibbeln et al. (2007)	Scale developed by the ALSPAC (items from Denver Developmental Screening Test)	Strengths and Difficulties Questionnaire; Child Behavior Checklist; IQ	Low maternal seafood intake (less than 340g per week) increased the risk of children being in the lowest verbal intelligence quartile and having other suboptimum development outcomes	Advice to limit seafood could be problematic, as children whose mothers consumed more than 340g per week performed better	Social differences between groups may have been a confounding variable; benefits may be due to other aspects of good nutrition than seafood intake	Medical Research Council; Wellcome trust; University of Bristol; UK government departments; medical charities; “other sources”
Hurtado et al. (2015)	Bayley Scales of Infant Development, second edition (BSID-II);	Maternal dietary intake (assessed with food frequency questionnaire) FA	No significant differences between intervention and control group	While the intervention increased both maternal and infant FA status, it did not	Limited sample size/ ability to evaluate neurodevelopment outcomes	Not reported; one author declared a conflict of interest as an employee of

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	Mental Development Index (MDI)	levels in mother's milk, plasma, placenta, and erythrocytes		produce expected neurodevelopment effects		Lactalis Puleva (dairy industry)
Makrides et al. (2010)	Cognitive and Language Scales of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)	Edinburgh Postnatal Depression Scale (EPDS) to measure maternal depression	While mean cognitive scores of children did not differ between the groups, the intervention group did exhibit less cognitive development delays than the control group	Need cognitive outcomes at later ages to clarify longevity of effects; gender differences should be addressed in more detail	No assessment of dietary intake	Australian National Health and Medical Research Council
Mendez et al. (2009)	McCarthy Scales of Children's Abilities (MCSA)		Maternal fish consumption more that 2-3 times per week correlated with significantly higher MCSA subscales, but only among children breastfed for less than 6 months	Moderately high fish intake during pregnancy appears to confer positive benefits among infants breastfed for less than 6 months	Further research on breastfeeding duration as a mechanism require	Spanish Ministry of Health; Instituto de Salud Carlos III; 'Fundació La Caixa'; European Com mission
Mulder et al. (2018)	K-ABC	Subject characteristics, dietary analysis, biochemical analysis	No differences in mean test performance or achieving scores in the upper quartile for performance on any of the tests assessed between groups; maternal DHA level associated with higher language/short-term memory scales	Despite having found differences in neurodevelopment test scores at 18 months of age, these benefits may not have lasted or may have been confounded by other variables by the time the children reached this age	Potentially insufficient design to detect DHA insufficiency; benefits may be confounded by other variables by this age	Canadian Institutes for Health Research
Oken et al. (2005)	Novelty preference on visual recognition memory (VRM)	Hair mercury assay	Higher fish intake was found to correlate with higher infant cognition levels; however, higher mercury levels were associated with lower cognition	Women should aim to consume low-mercury sources of fish during pregnancy for optimal infant cognition outcomes	Sample included many highly educated, white, and high SES mothers, so generalization should be undertaken with caution	Harvard Medical School; Harvard Pilgrim Health Care Foundation; National Institutes of Health
Ostadrahimi et al. (2018)	Age and stages questionnaire (ASQ-2)	Weight, height, and head circumference at birth	Of the five neurodevelopment domains assessed at each age, only the communication domain was found to have a positive correlation with fish oil supplementation, and only at 4 months of age	Further studies should be conducted with a broader population, particularly in contexts where consumption of fish tends to be low	Small sample size; dosage may have been inadequate, and cognitive measures may have been insufficiently sensitive	Research Vice-chancellor, Tabriz University of Medical Sciences
Ramakrishnan et al. (2016)	McCarthy Scales of Children's Abilities (MSCA)	The parental scale of the Behavioral Assessment System for Children, Second Edition (BASC-2), and	No significant differences on the MSCA subscales or mean general cognitive score. Higher	Among children with less stimulating home environments, DHA supplementation can have a particularly	Lack of data on child's learning environment at follow-up	NIH and the March of Dimes Foundation

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		the Conners' Kiddie Continuous Performance Test (K-CPT)	DHA levels correlated with less effect of the home environment; children in the intervention group had fewer omissions on the K-CPT.	important role in cognitive development; DHA supplementation can have positive effects on measures of attention and executive functioning		
Rees et al. (2019)	Cognition, visual acuity, habituation, and visual attention	n/s	DHA levels were found to be significantly correlated with visual acuity, even after adjusting for birth weight. There were no differences in habituation levels or visual attention levels	Empirical support for DHA supplementation remains inconclusive	Women of high SES levels more likely to participate; higher breastfeeding rates than general population; use of an FFQ rather than intervention	The Biotechnology and Biological Sciences Research Council and Mead Johnson Nutrition (industry)
Steer et al. (2013)	Wechsler Intelligence Scale for Children	*FADS* genotype analysis	Higher AA and DHA levels associated with higher IQ	*FADS* genes may have a significant role in synthesis of these FAs, and should be assessed in further research	Selective dropout (of socially/economically disadvantaged participants)	National Oceanic and Atmospheric Administration; Commission of the European Communities' Seventh Framework Programme NUTRIMENTHE; National Institute on Alcohol Abuse and Alcoholism
van Goor et al. (2010)	Standardized neonatal neurological examination at 2 weeks	Assessment of general movement quality at 2 and 12 weeks	Infants in the DHA group exhibited more abnormal movements than those in the DHA and AA and the control groups at 2 weeks; at 12 weeks, this result was repeated, but with a more significant difference between the groups	AA rather than DHA may be associated with general movement quality, and that DHA/AA balance during pregnancy is important to consider	Small sample size	FrieslandCampina, The Netherlands (dairy industry)
Vollet et al. (2007)	Ages and Stages Questionnaire (ASQ)–fine motor, gross motor, communication, personal–social functioning and problem solving domains		Maternal fish oil supplementation was related to lower risk of failing the problem solving domain of the ASQ in children up to 3 years	Prenatal fish oil supplementation may be beneficial	Limited information on dose/supplementation frequency; maternal reporting on ASQ may have introduced bias	Intramural Research Program of the Eunice Kennedy Shriver National Institute of Child Health and Human Development

overestimated effect sizes, and those of some smaller studies that have reported positive outcomes.

The studies included in this review that did yield positive outcomes of supplementation focused on communication and language, attentional tasks, and visual development. However, results in those areas are also mixed. Further, most studies that included a long-term follow-up largely reported that, even when positive outcomes were identified at a short-term follow-up, these outcomes often failed to persist at longer-term assessments.

Communication and Language. Several studies that assessed cognitive measures identified positive outcomes of *n*-3 LC PUFA supplementation and communication and language. The results of an RCT conducted in Iran found prenatal fish oil supplementation to be beneficial for neurodevelopment, but only in the communication domain, among infants at 4 months.[33] Similarly, although Mulder et al. did not report childhood neurodevelopment benefits of supplementation *in-utero*, the Authors did find higher maternal DHA level to be correlated to higher language scores on the K-ABC at 5-6 years of age.[34] While Colombo et al. found maternal blood DHA to correlate with higher verbal IQ at 5-6 years, this was not the case after controlling for the socioeconomic status.[35]

Attentional Tasks. One of the key findings for this cognitive developmental phase is the indication that prenatal supplementation with *n*-3 LC PUFAs has positive effects on infantile attention. Notably, the results of a large RCT (the Kansas University DHA Outcomes Study [KUDOS]) that assessed visual habituation among 4-, 6-, and 9-month-old infants whose mothers had been prenatally supplemented with DHA, indicate that maternal DHA supplementation correlated with improved performance on sustained attention and behavioral state tests during the first year of life.[36] In a secondary analysis of the DOMINO trial assessing the prenatal effects of DHA on working memory and inhibitory control (WMIC), no difference between the control and the treatment group were observed.[9]

While the results of the study by Ramakrishnan et al. did not indicate an effect of supplementation on general cognitive scores or MSCA subscales, children in the intervention group did make fewer omissions on the Conners' Kiddie Continuous Performance Test (K-CPT), which is used to measure attention.[14] The results of that study also indicate that *n*-3 LC PUFA supplementation attenuated the effect of home environment on cognition, suggesting the importance of DHA supplementation for children with less stimulating home environments.

Visual Development. In addition to its role in fetal brain tissue development, *n*-3 LC PUFAs play a significant role in retinal development; therefore, several studies have addressed prenatal *n*-3 supplementation in relation to visual acuity and cognitive-associated visual and attention tasks. Dunstan et al. found hand-eye coordination scores on the Griffiths Mental Development Scales (GMDS) to be correlated with cord blood *n*-3 LC PUFA levels.[17] In Hurtado et al. study there was not a correlation between supplementation with *n*-3 LC PUFAs during pregnancy or during lactation on neurodevelopment outcomes, or on visual acuity for the sample as a whole.[37] However, when stratification was done by gender, supplementation did cause visual acuity to improve for boys, but not for girls. Rees et al[15] conducted a visual acuity test and found that children whose mothers were in the moderate DHA intake group performed the best on this measure at 9 months, and that this finding was only significant in relation to third-trimester DHA levels.[15] However, the results did not indicate any significant difference in habituation and visual attention levels in relation to DHA levels.

Long-Term Effects. Although several studies found *n*-3 LC PUFA supplementation having beneficial effects during follow-up assessment conducted on younger children, reported controversial outcome with more negligible results. A follow-up to the Nutraceuticals for a Healthier Life (NUHEAL) cohort found that, at 6.5 years of age, prenatal DHA supplementation (500 mg DHA daily) did not correlate with K-ABC scores.[16] Similarly, a long-term follow-up to the KUDOS study revealed that, while prenatal DHA supplementation produced positive attention development outcomes during the first year of life, positive effects tended to dissipate at older ages.[35] For example, a significant correlation between supplementation and rule learning and flexibility was seen at 36 months, but not at older ages. Correlations between supplementation and attention and spatial memory that were observed at 24 and 36 months did not persist at older ages, and the significance of these findings decreased when the researchers controlled for sex and task variables. Also, while maternal blood DHA level during pregnancy correlated with higher IQ at 5-6 years of age, this finding disappeared entirely when the researchers controlled for SES.[35] The lack of long-term effects may have been due to the fact that both placebo and intervention groups obtained sufficient levels of LC PUFAs for cognitive development postnatally.

Similarly, although Mulder et al. found DHA insufficiency during gestation to be associated with risk of failing to achieve high neurodevelopmental test scores at 18 months of age, by 5.75 years of age, these results had dissipated.[34] However, maternal DHA status was related to child scores on some language and short-term memory scales of the K-ABC.

Helland at al. found that, while higher umbilical plasma DHA level did correlate with longer length of gestation, the groups did not show any cognitive differences at 6- or 9-

month follow-ups.[18] While the original study by Helland et al. did not report a correlation between cod liver oil supplementation during pregnancy and lactation and scores on the Fagan test for novelty preference at 6 or 9 months of age, a follow-up study on the original cohort reveled that, at 4 years of age, the children in the cod liver oil group scored an average of 4.1 points higher on the mental processing composite of the K-ABC.[21] While this result suggests that *n*-3 LC PUFA supplementation improves the intelligence of children at the age of 4, the researchers were unable to discern whether this result should be attributed to supplementation during pregnancy, lactation, or both. In a second follow-up study, however, Helland et al. did not find a difference in intelligence scores for children at 7 years of age, excepting insignificantly higher sequential processing scores among members of the intervention group.[19] However, by this time, the effects of supplementation may have been diluted by other diet and lifestyle factors; parental education level was also identified as a significant confounding variable.

Confounding Variables. In some cases, demographic variables were found to potentially skewing study results. For example, a secondary analysis of the DOMInO trial was conducted to assess whether maternal smoking status, maternal education, and socioeconomic status mediated the results. The adverse effects of smoking tended to negate the positive effects of DHA supplementation during pregnancy, and 18-month Bayley-III cognitive composite scores were higher for children in the DHA supplementation group, but only when their mothers had not completed further education.[9]

Supplementation During Infancy

In the 26 included studies assessing the effects of *n*-3 LC PUFA supplementation during infancy, the non-intervention studies featured analysis of FA levels in maternal human milk, cord levels, and supplementation via formula; supplementation studies featured maternal *n*-3 supplementation; supplemented human milk; supplemented formula; or direct supplementation to the infant independent of feeding. FA supplementation sources included fish oil, borage oil, and egg yolk, and various ratios of DHA, EPA, and AA (see Table 3 for more detail).[38-50] Sample sizes ranged from 52 to 604, and intervention lengths ranged from 9 weeks to 1 year. Ten of these studies were wholly or partially funded by organizations with interests in infant formula manufacturing or nutritional supplements.

The majority of studies were conducted in high-income countries where LC PUFA levels are often already sufficient, and numerous authors mentioned the possibility of a threshold/lack of deficiency as a potential explanation for their null results. The study by van der Merwe et al. is unique in having been conducted in a low-income country where infants were presumably more likely to suffer from adverse effects from *n*-3 LC PUFA deficiencies.[51] While no cognitive effects were reported, and maternal human milk FA levels were higher than anticipated, that study does highlight the issues with conducting research among affluent populations and in countries with high fish intake levels, as cognitive differences may be more detectable when deficiencies are present Table 4.

In general, LC PUFA supplementation during the early neonatal phase is done by supplementing lactating mothers or providing infant supplementation through DHA-containing formula or supplemented human milk. Effects of direct LC PUFA supplementation has been tested by Meldrum et al. which supplemented infants between birth and 6 months with a high-dose DHA-enriched ethyl ester Fatty Oil (FO).[52] Van der Merwe et al. also administered FO to the infant before breastfeeding.[51] Both studies failed to show any difference between treated group and control, however Meldrum et al. reported some benefits to early communicative development Table 5.

Dalmeijer et al. assessed the potential role of PUFAs benefits during breastfeeding, comparing with a control non-breastfed cohort (at the time of the study, formulas did not include PUFAs in the Netherlands). In 3 months old infants the results indicated some correlation between DHA level in human milk and higher scores on the Cito school standardized test; however, this was only true of girls, which indicates that sex-specific differences in ability to metabolize *n*-3 LC PUFAs require further investigation.[53]

Supplements in Very Low Birth Weight Infants. FA insufficiency during the third-trimester has been correlated to fetal brain development, premature birth, and very low birth weight (VLBW). Considering that VLBW children have increased risk of behavioral problems, Almaas et al. suggested that DHA supplement to VLBW infants would influence cerebral white matter and improve behavioral outcome. Results did not indicate significant differences between control and intervention groups for both the outcomes.[2]

Henriksen et al. tested the effect of DHA and AA supplementation in 129 VLBW infants fed human milk. The follow-up lasted 8 years, and whereas no differences in growth or

Table 3.

Supplementation during Infancy: Study Type and Participant Characteristics.

	Study type	Type/dosage of PUFAs	*N*	Length of intervention	Participant age range	Population characteristics
Almaas et al. (2016)	RCT	.5 mL oil (DHA/AA or placebo) per 100 mL of human milk	129 in original study; 92 participated in follow-up; 82 analyzed	9 weeks	Infancy during supplementation; follow-up at 8 years	Very low birth weight (VLBW; > 1500g)
Auestad et al. (2003)	RCT; follow-up study	.43% ARA and .12% DHA from egg-phospholipid; .23% DHA from fish oil; or control	157 in follow-up	1 week after birth–1 year	Follow-up at 39 months	n/s
Birch et al. (2000)	RCT	Formula supplemented with .35% DHA or with .36% DHA and .72% AA	56	From first 5 days of life to 17 weeks	Infancy during supplementation; cognitive testing at 18 months	Term infants
Birch et al. (2007)	RCT	Formula supplemented with .35% DHA or with .36% DHA and .72% ARA	52	17 weeks	Infancy during supplementation; follow-up at 4 years	Singleton infants with appropriate birth weights
Cheatham et al. (2011)	RCT	Lactating mothers supplemented with 1.5 g *n*-3 LC PUFA fish oil per day	122 mothers randomized; 98 children tested at age 7	First 4 months of lactation	Infancy during maternal supplementation; cognitive testing at 2.5 and 7 years	Women in 36th week of pregnancy with lower than median fish consumption (53 with high fish consumption also participated as a reference group)
Collins et al. (2015)	Follow-up of RCT	DHA rich tuna oil to achieve a human milk HA concentration of around 1%	604	40 weeks from first enteral feed	Infancy during original study; 7 years at follow-up	Born <33 weeks' gestation
Dalmeijer et al. (2016)	Observational cohort	Non-intervention (FA levels in human milk analyzed)	227 non-breastfed children (control); 157 breastfed children	Non-interventional	Human milk samples collected when children were 3 months; school performance data gathered at 12 years	n/s
de Jong et al. (2010)	RCT	Breast feeding; standard formula; or formula supplemented	474	2 months	Infancy; follow-up at 9 years	n/s

(continued)

Table 3. (continued)

		with 0·45% AA and 0·30% DHA				
de Jong et al. (2015)	RCT	Breast feeding; standard formula; or formula supplemented with 0·45% AA and 0·30% DHA	235	2 months	Infancy; follow-up at 9 years	n/s
Drover et al. (2011)	RCT	Control (0% DHA), .32% DHA, .64% DHA, or .96% DHA	181	12 months	Infancy; follow-up at 18 months	Children who had enrolled in the DIAMOND study
Fewtrell et al. (2004)	RCT	Unsupplemented or LC PUFA supplemented (borage oil and tuna fish oil) formula	238	To 9 months after term	Infancy; follow-up at 18 months	Preterm (<35 weeks, <2000 g birth weight)
Gale et al. (2010)	Prospective cohort	Breastfeeding or DHA-supplemented formula	241	Non-intervention; first 6 months	Infancy; follow-up at 4 years	Singleton live births to women in the Southampton Women's Survey
Henriksen et al. (2008)	RCT	31 mg AA and 32 mg DHA (supplemented human milk)	141 randomized; 129 completed	From 1 week after birth to discharge from the hospital (an average of 9 weeks)	Infancy; follow-up at 6 months	Birth weights of <1500 g
Henriksen et al. (2016)	RCT (follow-up)	31 mg AA and 32 mg DHA (supplemented human milk)	98 children participated in 8-year follow-up	From 1 week after birth to discharge from the hospital (an average of 9 weeks)	Infancy; follow-up at 8 years	Birth weights of <1500 g
Isaacs et al. (2011)	RCT	.5% DHA from borage and fish oils (supplemented formula)	107	First 9 months after birth	Infancy; follow-up at 10 years	Preterm infants
Jacobson et al. (2008)	Observational	Cord and maternal plasma and milk	109	Non-intervention	Assessed at 6 and 11 months	Residents of Arctic Quebec
Jensen et al. (2005)	RCT	approximately200 mg DHA/day	83 in DHA and 77 in control group participated to 30-month follow-up	4 months	Assessed at 4, 8, 12, and 30 months	Women who planned to breastfeed exclusively
Jensen et al. (2010)	RCT	200 mg DHA/day from algal oil	60 in DHA and 59 in control at 5-year follow-up	4 months	Follow-up at 5 years	Women who planned to breastfeed exclusively
Kalhoff et al. (2020)	RCT	Dietary intervention; complementary food with rapeseed oil, oily fish, or corn oil	54 in rapeseed oil group; 48 in fish group; 58 in corn oil group	5^{th} to 7^{th} month through 10^{th} month	Infancy; assessed at 10 months of age	Healthy term infants; mothers willing to breastfeed

(continued)

Table 3. (continued)

Lauritzen et al. (2005)	RCT	4.5 g/day fish oil	122 with reported low fish intake; 53 with reported high fish intake	4 months	Infancy; assessed at 9 months, 1 and 2 years of age	Uncomplicated delivery; intention to breastfeed for at least 4 months
Lepping et al. (2018)	RCT	Control or formula with .64% of total fatty acids as ARA and .32%, .64%, or .96% DHA	159; 42 enrolled at follow-up	12 months	Infancy; follow-up at 9 years	Completed 12 months of formula feeding in parent trial; no serious health conditions
Liao et al. (2017)	RCT (follow-up of the DIAMOND clinical trial)	Formula with .64% of total fatty acids as AA and various concentrations of DHA (.32%, .64%, or .96%)	69	First 12 months of life	Infancy; follow-up at 5.5 years	Healthy, full-term, formula-fed, singleton-birth
Meldrum et al. (2012)	RCT	250 mg DHA and 60 mg EPA per day (direct infant supplementation)	287	Birth–6 months	Infancy; assessment at 18 months	Allergic pregnant women (those who consumed more than 3 fish meals per week/ 1000 mg FO per day were excluded); term infants
Westerberg et al. (2011)	RCT	32 mg DHA and 31 mg AA (supplemented human milk)	92	1 week after birth to discharge from hospital	Infancy; assessment at 20 months	Very low birth weight infants (<1500 g)
Willatts et al. (2013)	RCT	Egg yolk (approximately 70% LC PUFAs) added to formula	235	First 4 months of life	Infancy; follow-up at 6 years	Healthy term singletons
van der Merwe et al. (2013)	RCT	Fish oil with 200 mg DHA and 300 mg EPA per day (administered to the infant before breastfeeding)	172	3 months of age—9 months of age	Infancy; assessed at 1 year	All 3-month-old infants in the 16 largest villages of the West Kiang region of The Gambia

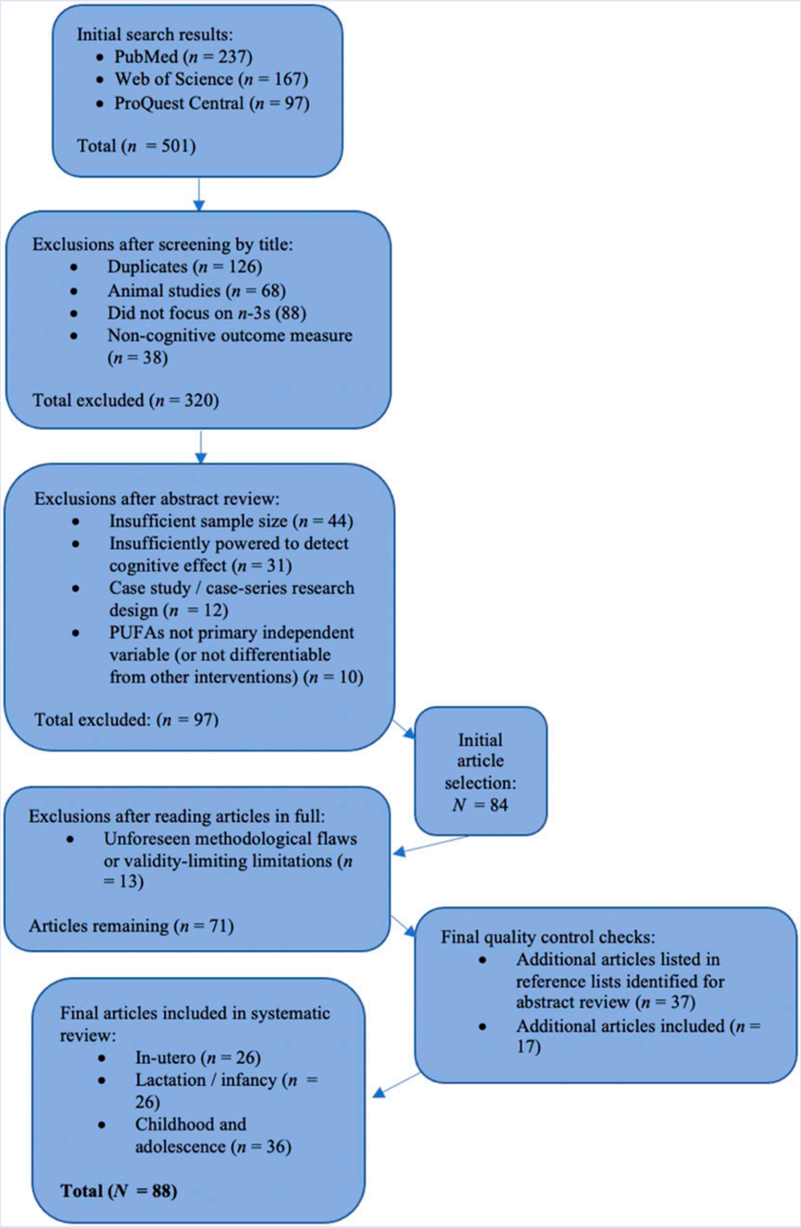
intelligence quotient (IQ) were found, blood DHA at 8 years was positively associated with IQ.[54]

Specific Outcomes of Interest. A limitation of previous research on LC PUFA supplementation during infancy is the lack in assessing specific cognitive domains. More recent studies conducted over the past 2 decades have endeavored the use of subscales and specific measures to access the cognitive function effects of FA supplementation during infancy. As such, the results of this review are organized according to the following cognitive domains: Communication, Intelligence, Working Memory, Programming During Brain Development, Attention, Problem Solving Table 6.

Communication. As addressed in the *in-utero* supplementation section, Ostadrahimi et al. conducted a study with a supplementation range including both *in-utero* and lactation periods, and found that—of five neurodevelopment domains assessed at each age—only the communication domain had a positive correlation with fish oil supplementation, and only at

Figure 1.

Literature search flow chart.



4 months of age.[33] However, negative language results have also been reported. Cheatham et al. found language and prosocial scores to be lower, only among boys, in the fish oil supplementation group than in the control group.[3]

While they did not find a significant effect of DHA supplementation during the first 9 months of life on overall cognitive function at 10 years of age, Isaacs et al. did find that girls in the supplemented group performed better on the reading and spelling measures of the Weschler Individual Achievement test.[55] However, both groups that received human milk scored higher on the Weschler subscales, again prompting the question of whether DHA or another factor associated with breastfeeding accounted for this correlation. While Meldrum et al. found that infants supplemented with FO exhibited higher gestural scores—important in relation to gesture as a precursor to language—the overall results of the study were inconclusive due to methodological issues including discrepant sample sizes across outcome measures and a high rate of correctly guessed group allocation, which may have introduced bias.[54]

Intelligence. In an early study on DHA supplementation during infancy, Birch et al. found that supplementation with DHA and AA during infancy correlated with an increase of 7 points on the BSID-II mental development index (MDI).[7] The cognitive and motor subscales of the MDI were significantly higher among both the DHA and DHA + AA groups, and the language scores were higher, but not significantly so. Isaacs et al. found that, while there were no overall differences in cognitive outcomes between the groups, 10-year-old girls in the supplemented group demonstrated improved performance in reading and spelling measures of the Weschler Individual Achievement test.[55]

While an 8-year follow-up study did not indicate any effect of supplementation during infancy on IQ, Henriksen et al. did find DHA level assessed at the time of the follow-up to correlate with higher IQ scores after correcting for maternal education and birth weight.[56] Willatts et al. did not find any difference in IQ scores among control or intervention (formula supplemented with egg yolk) group children at 6 years of age, but noted that the global testing measure may not be sufficiently sensitive to detect group differences.[11]

Working Memory. Henriksen et al. reported a significant benefit of DHA and AA supplementation

Table 4.

Supplementation during Infancy: Instrumentation and Results.

	Outcome measures		Results	Conclusion	Confounding variables/ limitations	Funding source
	Primary/cognitive	Secondary/other				
Almaas et al. (2016)	Behavioral outcomes measured with the Strengths and Difficulties Questionnaire [SDQ)] parent report version	Cerebral white matter microstructure (measured by diffusion tensor imaging [DTI])	No significant differences between the treatment and placebo groups on behavioral outcomes or cerebral white matter microstructure; the intervention group did exhibit higher fractional anisotropy in the corpus callosum	While the fractional anisotropy finding was non-significant, it may warrant additional research on this subject	Supplementation level may have been insufficient to produce long-term effects; confounding variables may have been present by age 8; exclusion of neurologically vulnerable groups	The Research Council of Norway, the South-Eastern Norway Regional Health Authority and the University of Oslo, Norway
Auestad et al. (2003)	Stanford-Binet Intelligence Scale Form L-M; the Peabody Picture Vocabulary Test-Revised (PPVT-R); and the Beery Visual-Motor Index test	Visual-motor function, red blood cell fatty acid levels, and the frequency of illnesses and hospitalizations since birth	At 39 months, the cognitive outcome measures did not differ among the intervention groups	Given that their previous results indicated lower vocabulary scores at 14 months among supplemented groups, the authors concluded that this follow-up confirmed that these results were either transient or anomalous, and that DHA + ARA supplementation in formula does support visual and cognitive development	Sample size	Ross Products Division, Abbott Laboratories, Columbus, Ohio
Birch et al. (2000)	BSID-II at 18 months	Blood fatty-acid composition, sweep visual evoked potential acuity, and forced-choice preferential looking acuity at 4 and 12 months	Mean increase of 7 points on the mental development index scale of the Bayley test for the DHA + AA group, and a trend toward more accelerated performance on the same subscale amount this group	The authors concluded that early dietary DHA supply correlated with improved performance on the MDI.	Forced-choice preferential looking acuity was not found to correlate with 18-month MDI scores, and may not have been an effective measure of cognitive development; BSID scores' ability to predict school-age performance may have been limited as the sample did not include a range of developmental speeds (most were within normal range)	NIH and Mead Johnson Nutrition (infant formula manufacturer)
Birch et al. (2007)	Wechsler preschool and primary scale of intelligence	HOTV visual acuity	In visual acuity and IQ maturation, the supplemented groups had similar scores to the breast-fed group	DHA + ARA supplemented formula is a comparable alternative to breast feeding in terms of cognitive outcomes	Maternal variables associated with decision to breastfeed	NIH
Cheatham et al. (2011)	Infant Planning Test (means end problem solving); Woodcock Johnson Tests of Cognitive Abilities III (speed of cognitive processing); Stroop task (higher-order cognitive functioning)	Socio-emotional functioning (Strength and Difficulties Questionnaire)	No differences between groups for the processing speed measure; the prosocial score on the SDQ tended to be higher in the control group, which was significant when only boys' results were included. Maternal LC PUFA intake level and maternal education level were significant predictors for speed of processing	The authors noted that lower language comprehension scores among boys in the fish oil group may have contributed to their lower prosocial scores, but did not discern why fish oil supplementation would have produced a negative effect on these measures	Sample size may have been too small to detect small effect size; results may not be generalizable given the typically high fish intake among Danish people; not powered to detect a potential inverted-U effect of FO supplementation	Food Technology Research and Development Programme, Denmark (FØTEK)
Collins et al. (2015)	Full Scale IQ of the Wechsler Abbreviated Scale of Intelligence	Subtests of: of Everyday Attention for Children; Rey Auditory Verbal Learning Test; Test of Visual Perceptual Skill; Wide Range Achievement Test. Conners 3rd Edition ADHD Index; Strengths and Difficulties Questionnaire	No effect of supplementation on IQ, attention, executive function, behavior, visual-spatial perceptual skills, educational progress, or quality of life at 7 years of age	No long-term benefit of this type of supplementation	Variations in maternal compliance/DHA concentrations in human milk; no teacher assessment of children's cognitive function	National Health and Medical Research Council, Australia; Mead Johnson Nutrition
Dalmeijer et al. (2016)	Cito standardized school achievement test and teachers' assessment of secondary school potential	n/a	No association between Cito score and LC PUFAs among boys; girls who received human milk with high amounts of *n*-3 LC PUFAs scored higher on the Cito test	While some of this effect can be explained by sociodemographic factors, high levels of PUFA content, particularly DHA, in human milk can produce cognitive benefits among girls at the age of 12	Only one sample of human milk obtained; not known whether LC PUFA levels remained consistent throughout lactation; sample size sufficient to evaluate results based on sex, but not to have more than two groups	Netherlands Organization for Health Research and Development; Netherlands Organization for Scientific Research; Netherlands Asthma Fund; Netherlands Ministry of Spatial Planning, Housing, and the Environment; Netherlands

(continued)

Table 4. (continued)

						Ministry of Health, Welfare, and Sport
de Jong et al. (2010)	Neurological examination according to Touwen	Obstetrical Optimality Score; maternal intelligence; social condition	Cognitive outcome measures (Neurological Optimality Score) did not differ between the two formula groups	Postnatal *n*-3 supplementation does not have an effect at 9 years of age	Attrition rates	Food Quality and Safety Priority of the Sixth Framework Programme for Research and Technical Development of the European Community
de Jong et al. (2015)	Minor neurological dysfunction	IQ; behavioral development	Among boys, those with minor neurological dysfunction were more likely to have had lower umbilical vein DHA levels	Higher levels of DHA at birth correlate with lower levels of neurological dysfunction at 9 years of age, only among boys	Attrition rates	Food Quality and Safety Priority of the Sixth Framework Programme for Research and Technical Development of the European Community
Drover et al. (2011)	Bayley Scales of Infant Development, 2nd edition (BSID II)	Fatty acid analysis	No significant between-group cognitive difference. When all intervention groups together were compared to the control group, supplemented children had better Mental Development Index scores	The results indicate a threshold effect at .32% concentration of DHA in formula, which is beneficial for cognitive development up to 18 months	There are several alternative explanations (other than increased DHA status) for these findings; further research is required	Mead Johnson Nutrition
Fewtrell et al. (2004)	Bayley Mental and Psychomotor Indexes	Growth; safety and tolerance outcomes	No overall difference between groups in neurodevelopment outcomes; only among boys, those in the LC PUFA group had significantly higher mental development index scores than those in the control group	The supplementation proved to be safe and to have mental development index improvement implications for boys, and growth implications for all children	Global outcome measure tests may not have been sufficiently subtle	H. J. Heinz Company Ltd
Gale et al. (2010)	Wechsler Pre-School and Primary Scale of Intelligence; Test of Visual-Perceptual Skills (Non-Motor); Developmental Neuropsychological Assessment	Dietary assessment; maternal and child characteristics	Higher total and verbal IQ scores for children who were breast fed or fed with DHA-fortified formula than those fed unfortified formula	These results may be explained by maternal or family characteristics	Women who took part in the survey tended to be better education with a higher SES	Medical Research Council and the Dunhill Medical Trust
Henriksen et al. (2008)	Ages and Stages Questionnaire (ASQ)	Event related potentials—recognition memory	Plasma DHA levels increased by 12% in the treatment group and decreased by 9% in the control group during the intervention; the intervention group scored higher on the problem solving subtest of the ASQ. The results of the event-related potentials testing showed a significant benefit on working memory in the intervention group	DHA and/or AA have cognitive benefits in terms of problem solving and working memory at 6 months of age	Low power for detecting ASQ differences; possibility of type 2 errors	Norwegian Foundation for Health and Rehabilitation; Johan Throne Holst Foundation for Nutrition Research; Freia Medical Research Foundation; Research Council of Norway; Thematic Program on Perinatal Nutrition, Faculty of Medicine, University of Oslo
Henriksen et al. (2016)	Wechsler Abbreviated Scale of Intelligence	Growth measures and blood biomarkers	While supplementation with DHA and AA produced lower levels of insulin-like growth factor-1 (IGF-1) at follow-up, it did not affect weight, length, or IQ; however, blood DHA levels at follow-up did correlated with higher IQ after correcting for birth weight and maternal education	The results are in alignment with those of previous studies, which did not find significant long-term effects of LC-PUFA supplementation, but do indicate that DHA should be supplied specifically throughout life	Number of participants inhibits subgroup analyses and many have increased the risk of type 2 errors	Research Council of Norway, the South-Eastern Norway Regional Health Authority, and the University of Oslo
Isaacs et al. (2011)	Wechsler Abbreviated Scale of Intelligence, the Neuropsychological Test for Children, the word pairs test from the Children's Memory Scale (to assess association learning ,which is related to the hippocampus), the Weschler Individual Achievement Test, the Test of Everyday Attention for Children, and the Behavioural	n/a	10-year-old girls in the supplemented group demonstrated improved performance in reading and spelling measures of the Weschler Individual Achievement test	The results also indicate that both groups that received human milk scored higher on subscales of the Weschler Individual Achievement Test, again prompting the question of whether breastfeeding or PUFAs was the cause of the positive effect	Relatively small group numbers (low follow-up participation rate)	European Union Early Nutrition Programming Project, as part of the Sixth Framework Program; Heinz UK; two researchers received funding from infant feeding manufacturers

(continued)

Table 4. (continued)

	Assessment of the Dysexecutive Syndrome for Children					
Jacobson et al. (2008)	Teller Visual Acuity Card Test; Fagan Test of Infant Intelligence (6 months); and the same as well as the Bayley Scales of Infant Development, 2nd edition at 11 months	Demographic control variables	Higher cord DHA correlated with longer gestation, better visual acuity and novelty preference scores, and better Bayley Scale scores, but higher maternal milk DHA did not have any significant effect	The results confirm the third trimester as the crucial period for DHA accretion	Less precise measurement techniques available for breastfeeding than for prenatal intake, which may have affected the results	National Institute of Environmental Health Sciences; Indian and Northern Affairs, Canada; Health Canada; Hydro-Quebec; Joseph Young, Sr, Fund of the State of Michigan
Jensen et al. (2005)	Bayley Scales of Infant Development	Gesell Developmental Inventory; Clinical Linguistic and Auditory Milestone Scale; Clinical Adaptive Test	Bayley Psychomotor Development Index scores were higher in the supplemented group at 30 months of age	No other advantages, and none identified at testing before 30 months	Inadequate sensitivity of motor function tests early in life may have affected the results	US Department of Agriculture/National Research Initiative; Martek Biosciences Corp; Mead-Johnson Nutritionals
Jensen et al. (2010)	Bailey-Lovie acuity chart, transient visual evoked potential, sweep visual evoked potential testing		No differences between DHA and control groups at 5 years of age, except on the on the Sustained Attention Subscale of the Leiter International Performance Scale (in which supplemented children performed significantly better	DHA supplementation during infancy can have long-term effects on sustained attention	Attrition	Martek Biosciences Corp; U.S. Department of Agriculture/ National Research Initiative
Kalhoff et al. (2020)	Flash visual evoked potential (FVEP); Bayley Scales of Infant Development		No significant differences between intervention and control groups	This dietary intervention did not appear to influence either cognitive or visual development of infants at 10 months of age	Explorative evaluation of functional outcomes; sample size	Federal Ministry of Education and Research
Lauritzen et al. (2005)	Willatts Infant Planning Test; MacArthur Communicative Development Inventory		No effect on problem solving ability; word comprehension inversely associated with DHA level at 4 months	There may be a small adverse effect of supplementation on early language development, which may be transient	Lower than suspected power for outcome measures; not all participants were breastfed for the entire study period	Danish Research and Development Program for Food and Technology; BASF Aktiengesellschaft
Lepping et al. (2018)	Functional (fMRI, Flanker task), resting state (rsMRI), anatomic, and proton magnetic resonance spectroscopy (1H MRS)		Supplemented children showed more activity in anterior cingulate cortex (ACC) and parietal regions; greater connectivity between prefrontal and parietal regions in the .64% DHA group; greater white matter volume in ACC and parietal region for .32 and .64% groups	LCPUFA supplementation during infancy appears to have long-term effects on brain structure	Small sample size; some problems with children participating in the imaging studies	Mead Johnson Nutrition
Liao et al. (2018)	Group differences in behavior and event-related potentials (ERPs) while performing a task requiring response inhibition (Go/No-Go)	n/a	No significant difference in either accuracy or reaction time between the dose levels; while the intervention groups collectively tended to have better reaction times than the control group, these results were not significant; participants in the intervention groups exhibited activation of a larger, synchronized neuronal network than the control group	Early LC PUFA supplementation can have an important programming effect on the brain during development	Smaller sample size/ participants lost to follow-up	Mead Johnson Nutrition
Meldrum et al. (2012)	Bayley Scales of Infant and Toddler Development and the Child Behavior Checklist; Macarthur–Bates Communicative Development Inventory (language development)	Allergy outcomes	No effect on neurodevelopmental skills on Bayley Scales; more observed anxious/depressed behaviors among FO group; FO group performed better in language assessments, with a higher number of gestures	While the results do not fully support the hypothesis, further studies with larger sample sizes are warranted	The majority of participants correctly guessed group allocation—potential for bias; discrepant sample sizes for different assessment measures	National Health and Medical Research Council (NHMRC) of Australia
Westerberg et al. (2011)	Bayley MDI and Ages and Stages questionnaire	Free-play session to assess attention	No significant between-group differences on the Bayley scale or the ASQ; in the free-play sessions, the intervention group demonstrated more time sequences with a high level of	The results do not fully support the hypothesis, and small sample size means that their significance is limited; further study is required to discern the	High level of follow-up attrition; lack of statistical power to detect small between-group differences	Norwegian Foundation for Health and Rehabilitation; Johan Throne Holst Foundation for Nutrition Research; Faculty of Medicine at the University of

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Table 4. (continued)

			attention and higher levels of sustained attention than the control group	impact of supplementation on attention		Oslo; Freia Medical Research Foundation; Research Council of Norway
Willatts et al. (2013)	IQ attention control (Day-Night Test), and speed of processing on the Matching Familiar Figures Test (MFFT)		The results did not indicate any difference between the two groups in terms of IQ scores. On the impulsivity/information processing efficiency test (the MFFT), response latencies of children in the intervention group were shorter	Supplementation with LC PUFAs does not appear to improve problem solving ability, but does improve its efficiency. The LC PUFAs in this study were derived from egg yolks (and therefore in phospholipid rather than triglyceride form), and DHA was at the lower end of the recommended amounts scale, which may have affected the result	Potential selection bias (children in follow-up had higher birth weight/several other advantageous demographic factors, making them less susceptible to developmental delays)	Numico Research, Friedrichsdorf, Germany
van der Merwe et al. (2013)	Willatts' 2-step Infant Planning Test, and a single-object task attention test	Anthropometric measures; gut integrity	There were no significant differences on either of these cognitive outcome measures, but the intervention did result in a significant increase in mid-upper arm circumference	Maternal human milk LC PUFA levels in The Gambia appeared, unexpectedly, to be sufficiently high, which may have affected the study results; further studies should address low-income settings	Sufficient maternal *n*-3 PUFA levels; intervention may have been more effective if infants who were not breastfed had been targeted	UK Medical Research Council, the Overseas Research Students Awards Scheme, and the Ernest Oppenheimer Memorial Trust

during infancy on working memory, tested using event related potentials.[56] They also reported that the test required infants to be relatively calm, and that agitated infants were excluded from the analyzed sample.Programming During Brain Development

Liao et al. found that participants in the intervention groups exhibited activation of a larger, synchronized neuronal network than the control group, suggesting that early LC PUFA supplementation can have an important programming effect on the brain during development.[57]

Attention. Westerberg et al. found that intervention group infants demonstrated more time sequences with a high level of attention during free play sessions than the control group, as well as higher levels of sustained attention among members of the intervention group.[58] Higher DHA levels at hospital discharge did correlate with better sustained attention levels and MDI scores, but due to loss to follow-up, the study's ability to detect small between-group differences was limited, and the results may be attributable to chance. Willatts et al. did not find LC PUFA supplementation during infancy to affect scores on an attention control test.[11] However, the results did indicate an effect of supplementation on the speed of information processing, with shorter response latencies on the Matching Familiar Figures Test among members of the intervention group. Jensen et al. found that children whose mothers received modest DHA supplementation during breastfeeding for the first 4 months after delivery performed better on a test of sustained attention at 5 years of age.[59]

Problem Solving. In a study supplementing infant with formula containing DHA and AA, Willatts et al. noted that supplementation with LC PUFAs did not improve problem solving ability, but did improve its efficiency.[11] In addition, Henriksen et al. found that supplementation significantly improved performance on the problem solving subset of the Ages and Stages Questionnaire.[56]

Childhood and Adolescence

In the 36 studies[60-95] described in tables 5 and 6 that met the inclusion criteria for this systematic review intervention lengths ranged from 3 weeks to 4.5 years. The main source of *n*-3 LC PUFA was primarily fish or algal oil. Subjects in the reviewed studies divided between healthy developing populations (n = 13) and those with clinical characteristics: history of asthma (n = 1), ADHD (n = 10), potential DHA deficiency (either as a result of preterm birth or low *n*-3 index; n = 2), ASD (n = 1), mood disorders (n = 1), or phenylketonuria (n = 1), iron deficiency (n = 1), malnutrition (n = 1); or below average reading level (n = 2) Figure 1.

While significant attention has been given to the importance of LC PUFA level during gestation and the first year of life, less is known about its role in subsequent development. Specifically, the period from 12 months to 24 months remains a significant developmental period, which is also marked by dietary changes that can lead to deficiencies. Devlin et al. investigated the cognitive effect of DHA and ARA

Table 5.

Supplementation During Childhood and Adolescence: Study Type and Participant Characteristics.

	Study type	Type/dosage of PUFAs	*N*	Length of intervention	Participant age range	Population Characteristics
Åberg et al. (2009)	Highly powered observational	Food frequency questionnaire data	3972	Non-intervention; cognitive performance assessed 3 years after questionnaire data collected	15 at time of questionnaire	15-year-old males in western Sweden
Baumgartner et al. (2012)	2-by-2 factorial trial	420 mg DHA/80 mg EPA; iron; placebo; or combination	321	8.5 months	6-11	Children with iron deficiency
Bos et al. (2015)	RCT	650 mg EPA and 650 mg DHA	40	16 weeks	8-14	Boys with ADHD
Brew et al. (2015)	Secondary analysis of the Childhood Asthma Prevention Study RCT	Tuna fish oil with 37% LC PUFAs (added to formula or food)	239	From the age of 6 months through age 5	8-14 years at follow-up	History of asthma
Cornu et al. (2018)	RCT	DHA and EPA (dosage in alignment with age group guidelines/ previous studies) or placebo	71 in treatment group; 77 in placebo	3 months	6-15	Children with ADHD
Crippa et al. (2019)	RCT	500 mg algal DHA/ day	50	6 months	7-14	Confirmed ADHD diagnosis; drug-naïve; no *n*-3 or *n*-5 supplement consumption in the previous 3 months
Dalton et al. (2009)	RCT	Fish-flour bread spread	193	6 months	7-9	Students in grade 2 at a primary school serving a community with low socioeconomic status and of mixed ancestry from the Northern Cape Province of South Africa
Darcey et al. (2019)	Longitudinal	Food frequency questionnaire	87	Non-intervention	13.3 ± 1.1 years	—
de Groot et al. (2012)	Observational	Non-intervention; fish consumption data	700	Non-intervention	12-18	Dutch high school students

(continued)

Table 5. (continued)

Demmelmair et al. (2018)	RCT	Between 0 and 127 mg of DHA (from algal oil) per day	109	6 months	5-13	Diagnosis of phenylketonuria (PKU)
Devlin et al. (2017)	RCT	200 mg of DHA per day and 200 mg of ARA per day	133	1 year	12-24 months of age	Healthy term toddlers
Handeland et al. (2017)	RCT	Either fatty fish meals three times per week (90 g fish per serving), meat meals three times per week, or fish oil supplementation (158 mg EPA, 105 mg DHA, and 13 mg DPA	426		14-15 years of age	9th-graders at 8 participating schools
Kean et al. (2017)	RCT	Green-lipped mussel extract	144	14 weeks	6-14	DSM-IV ADHD rating score of greater than 15
Keim et al. (2018)	RCT	200 mg of DHA (from Schizochytrium species algal oil) and 200 mg of AA (from fungal *Mortierella alpina* oil)	377	6 months	12-24 months	Preterm children (born at less than 35 weeks' gestation)
Kim et al. (2010)	Observational	Food frequency questionnaire	10 837	Non-intervention	15	Living in Västra Götaland region of Sweden
Kennedy et al. (2009)	RCT	400 mg or 1000 mg DHA/day	90	8 weeks	10-12	Healthy
Kirby et al. (2010)	RCT	400 mg fish oil; 260 mg of which provided v-3 nutrients, including DHA (200 mg) and EPA (28 mg)	450	16 weeks	8-10	Typically developing
Mazahery et al. (2019)	RCT	Vitamin D3 (2000 IU/day), DHA (722 mg/day), both, or placebo	73	1 year	2.5-8	Medical diagnosis of ASD
Milte et al. (2012)	RCT	4 capsules/day with either: EPA-rich fish oil (EPA 1109 mg; DHA 108 mg); DHA-	90	4 months	7-12	Over 90th percentile score for ADHD symptoms

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Table 5. (continued)

		rich fish oil (EPA 264 mg and DHA 1032 mg), or safflower oil (LA 1467 mg)				
Milte et al. (2015)	RCT	EPA-rich fish oil, providing a total of 1109 mg EPA and 108 mg DHA or DHA-rich fish oil, providing 264 mg EPA and 1032 mg DHA	87	4 months	6-13	Diagnosis of ADHD or parent-rated symptoms >90th percentile on the Conners' Parent Rating Scale (CPRS; Conners, 2000) and parent-reported learning difficulties (described as literacy performance behind their year level at school)
Montgomery et al. (2013)	Observational	Non-intervention; whole blood fatty acid levels assessed	493	Non-intervention	7-9	Children from mainstream Oxfordshire schools with below average performance in reading
Øyen et al. (2018)	RCT	Herring or mackerel for lunch three times a week, while the control group received chicken, lamb, or beef; the meals included a mean concentration of .21 mg/g EPA + DHA in the meat group and 15.2 in the fish group	218	16 weeks	4-6	Children at the 13 participating schools from ages 4-6 with sufficient Norwegian language skills for cognitive testing
Parletta et al. (2013)	RCT	750 mg docosahexaenoic plus eicosapentaenoic acids, and 60 mg gamma linolenic acid/school day	409	20 weeks; one way crossover (assessed at baseline, 20, and 40 weeks)	3-13	Indigenous Australian children
Portillo-Reyes et al. (2014)	RCT		59	3 months	8-12	Mild to moderate malnutrition

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Table 5. (continued)

		3 capsules with 60 mg of DHA and 90 mg of EPA				
Raz et al. (2009)	RCT	600 mg EFA/day	73	7 weeks	7-13	ADHD diagnosis from a child psychiatrist
Richardson and Montgomery (2005)	RCT	Food supplement with *n*-3 and *n*-6 fatty acids	117	3 months	5-12	Children with developmental coordination disorder (DCD)
Richardson et al. (2012)	RCT	600 mg/day DHA (from algal oil)	362	16 weeks	7-9	Children underperforming in reading
Ryan and Nelson (2008)	RCT	400 mg DHA/day	175	4 months	4	Healthy; normal developmental milestones; did not consume more than 3 oz of fish more than twice per week or take omega-3 supplements
Sheppard and Cheatham (2013)	Observational	Non-intervention (three 24-hour diet recalls	70	n/a	7-9	7-9 years old, English speaking; no pervasive developmental issues
Sinn et al. (2008)	RCT	EPA (93 mg), DHA (29 mg) from 400 mg fish oil; alongside evening primrose oil	PUFA group = 129; placebo group = 104	15 weeks	7-12	Connors' ADHD index score
Sørensen et al. (2015)	Secondary analysis of the Optimal Well-Being, Development and Health for Danish Children through a Healthy New Nordic Diet School Meal Study	2 fish meals per week	726	3 weeks	8-11	Danish second- and third-grade children
Widenhorn-Müller et al. (2014)	RCT	600 mg EPA, 120 mg DHA	95	16 weeks	Average age of participants at the beginning of treatment was 8.86 years old for boys and 9.10 for girls	6-12 years of age, meeting DSM-IV criteria for the ADHD combined subtype (hyperactive–inattentive), the

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Table 5. (continued)

						primarily inattentive or the hyperactive/ impulsive subtype
van der Wurff et al. (2016)	Secondary analysis of the Food2Learn RCT	Non-intervention; Omega-3 index determined via finger prick blood sample	266	Non-intervention	13-15	Typically developing
van der Wurff et al. (2019)	RCT	400 mg EPA + DHA per day in cohort I; 800 mg EPA + DHA per day in cohort II	267	1 year	Mean = 14	Omega-3 index ≤5%
Vesco et al. (2018)	Secondary analysis of two RCTs	1.87 g *n*-3s daily (or two 50-minute psychoeducational psychotherapy sessions per week)	95	12 weeks	7-14	Diagnosis of depressive, cyclothymic, or bipolar disorder
Voigt et al. (2011)	RCT	345 mg DHA/day	63	4 months	6-12	Children with ADHD receiving effective maintenance therapy

supplementation in toddler. The author reported no effects on cognitive and language composite, but did find red blood cell ARA level to correlate with improved language scores.[60] Another study conducted with toddlers did not indicate positive outcomes of DHA and AA supplementation, and found some negative effects of supplementation on language development among all but the lowest birth weight and lowest SES groups.[61]

In a long-term study, Brew et al. attempted to discern whether FO supplementation from 6 months to 5 years of age correlated with children's scores on the NAPLAN.[62] Similar to studies assessing *in-utero* supplementation's effects on long-term cognitive outcomes, the results did not indicate that supplementation had any effect on scores. However, LC PUFA level at 8 years of age did correlate with test scores after correcting for birth weight, maternal age and education level. Similarly, in an adolescent population, Åberg et al. found that those who had consumed more than one fish meal per week at the age of 15 (assessed via questionnaire, had significantly higher cognitive performance levels in terms of composite, verbal, and visuospatial intelligence than those who had less, even after accounting for education level.[63]

In one study investigating the effects of omega-3 supplementation on children's learning and behavior, the authors reported equivocal results with a significant increase in DHA and EPA levels in both the placebo as well as the treatment group. Authors suggested that this may have been due to dietary changes based on increased awareness via information provided to participants' parents on the purpose of the study.[64]

Two important childhood and adolescence intervention studies—FINS-KIDS and FINS-TEENS—addressed the effect of dietarily supplied *n*-3 LC PUFAs from herring or mackerel meals three times per week, as opposed to meat meals three times per week. In the FINS-KIDS study, the meals included a mean concentration of .21 mg/g EPA + DHA in the meat group and 15.2 in the fish group, and caregivers filled out a food frequency questionnaire to provide information on non-intervention *n*-3 consumption.[65] After adjusting for dietary compliance, Øyen et al. found that the fish group demonstrated more WPPSI-III raw score improvement, as well as three subtests and the non-dominant hand 9-HPT test, but the overall results did not indicate improved general

Table 6.

Supplementation During Childhood and Adolescence: Instrumentation and Results.

	Outcome measure		Results	Conclusion	Confounding variables/ limitations	Funding source
	Primary/cognitive	Secondary/other				
Åberg et al. (2009)	Intelligence tests conducted as part of the Swedish military conscription examination		Compared to those who consumed fish meals less than once per week, those who consumed more than one fish meal per week had higher scores of combined intelligence 3 years later, as well as higher scores in verbal and visuospatial performance, even after accounting for education level	Fish intake has a significant effect on composite, visual, and visuospatial intelligence, measured 3 years later	Physical activity may have been a confounding variable; lack of information on diet other than fish	Swedish Society of Medicine; Department of Public Health at the Västra Götaland Region; Swedish Science Council
Baumgartner et al. (2012)	Hopkins Verbal Learning Test (HVLT) and subscales of the Kaufman Assessment Battery for Children		DHA/EPA did not produce a benefit on any of the cognitive tests, and appeared to have a negative impact on working memory	*n*-3 supplementation does not appear to have cognitive benefits for children with iron deficiency	Study period/dosage, and previous level of FAs in the population may have affected the results	Unilever Research and Development; Medicor Foundation, Vaduz; Principality of Liechtenstein; North-West University
Bos et al. (2015)	fMRI study with a traditional Go-NoGo paradigm	Parent-rated Child Behavior Checklist (CBCL) and Strengths and Weaknesses of ADHD symptoms and Normal behavior scale (SWAN); Essential Fatty Acids Questionnaire (EFAQ)	Supplementation improved parent-rated ADHD symptoms, but did not affect cognitive control or fMRI results	Omega-3 supplementation can complement other ADHD treatments	Some participants had changes to ADHD medication during the intervention period	Two authors are employees of Unilever
Brew et al. (2015)	National Assessment Program—Literacy and Numeracy (NAPLAN) scores		Supplementation did not improve long-term academic performance as measured by the NAPLAN; however, *n*-3 LC PUFA levels at 8 years of age did correlate with academic performance from between 8 and 14 years of age	Other variables (like maternal education and SES) may explain the correlation between LC PUFA levels at age 8 and test scores, in part because children's *n*-3 levels by that time were food- rather than supplement-derived	High attrition rates for follow-up; potential consequent introduction of selection bias	Not industry funded (individual authors supported by various NHMRC/Swedish Research Council Grants); one author declared an advisory board role with Novartis
Cornu et al. (20 180	Attention-Deficit Hyperactivity Disorder Rating Scale version 4	Alouette test; Test of Attentional Performance for Children; 48-item Conners Parent Rating Scale-Revised; Children's Depression Inventory—CDI	ADHD rating scale score reduction was more significant in the placebo than intervention group	Supplementation does not appear to produce a positive effect on ADHD symptoms	Did not measure blood levels	URGO laboratories
Crippa et al. (2019)	ADHD rating scale IV Parent Version–Investigator	Conners' Parent Rating Scale–R; Strengths and Difficulties Questionnaire (SDQ); Child Health Questionnaire; Clinical Global Impression—severity Scale; Amsterdam Neuropsychological Tasks	No differences between treatment groups identified for the primary outcome measure; DHA supplementation also produced a significant (though small) improvement in measures of focused attention	Small improvements in the CHQ Psychosocial summary and improved in parental ratings of emotional problems on SDQ indicate a limited potential benefit of *n*-3 supplementation among this population	Small sample size; underpowered to detect the effect of *n*-3 supplementation	Dietetic Metabolic Food srl. (prescription drug industry)
Dalton et al. (2009)	Hopkins Verbal Learning Test; Reading test; Spelling test	Biochemical analysis; blood samples	EPA and DHA significantly increased in the intervention group; as did	Dietary omega-3 supplementation improves	Mental performance may have been affected by other nutritional factors;	Department of Science and Technology Innovation Fund

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Table 6. (continued)

			scores on the Hopkins Verbal Learning Test Recognition, Discrimination Index, and Spelling test	children's memory and verbal learning	another component of the fish flour than DHA may have produced the improvements	
Darcey et al. (2019)	Behavior Rating Inventory of Executive Function; Go/No-Go Task	Kauffman Brief Intelligence Questionnaire; Pubertal Development Scale; family socioeconomic status	Higher omega-3 intake levels associated with caregiver-assessed inhibitory control, as well as task-based impulse control	Results also indicate poorer cortical development (based on activation in the dorsal anterior cingulate), indicating the importance of omega-3s in adolescent development	Food-frequency questionnaire relies on diet recall	NIH/NIAAA
de Groot et al. (2012)	End term grades; Amsterdam Vocabulary Test; Youth Self-Report		More fish intake (up to the recommended amount) correlated with higher end-term grades and better vocabulary	Adolescents should be advised to eat fish twice a week	Non-intervention; portion size not accounted for	n/s
Demmelmair et al. (2018)	Raven's Progressive Matrices (RPM)	Latencies of visually evoked potentials; Lincoln-Oseretzky Motor Development Scale was used to test fine and gross motor skills; glycerophospholipid (GPL) fatty acids measured	While amount of DHA in GPL increased proportionally to treatment group, there were no differences in cognitive and neurological functions	The researchers also evaluated fatty acid desaturase genotypes, and found that they were associated with AA levels and with DHA levels when accounting for previous ALA levels as a precursor to DHA	Smaller than expected sample size; inconsistencies measuring the Phe level; differences in test procedures across included centers	Commission of the European Communities, the Sixth Framework Programme NUTRIMENTHE; Nutricia (medical nutrition industry)
Devlin et al. (2017)	Bayley Scales of Infant and Toddler Development 3rd Edition (Bayley-III)	Beery–Buktenica Developmental Test of Visual–Motor Integration; measures of attention during play	No significant effects of supplementation identified on the primary cognitive function and language development measures; boys in the supplement group exhibited fewer inattention episodes than those in the control group; positive association between ARA levels in red blood cell phosphatidylethanolamine and cognition, only among boys; both boys' and girls' ARA levels correlated with their language scores	Future research should further investigate the ideal DHA and ARA levels for this age group using more sensitive measures of cognition	Outcome measures may have been insufficiently sensitive	DSM Nutritional Products (supplement manufacturer)
Handeland et al. (2017)	Attention performance measured by the d2 test of attention	Performance in a Norwegian reading and spelling test named "Kartleggeren" was assessed but not reported, due to considerable ceiling effects in nearly all outcomes at pre and post intervention. Mental health status was measured with the Strengths and Difficulties Questionnaire (SDQ)	The results of the d2 test of attention indicate that, for total performance and processing speed, the fish meal group scores were significantly higher than the supplement and meat groups. While omission errors decreased in the meat group, this finding was not significant after controlling for dietary compliance	The benefit of omega-3s on speed of cognition was identified even in individuals with low levels of dietary compliance, which should prompt careful interpretation of the results	No pure placebo group; low dietary compliance; only one cognitive outcome	The Norwegian Seafood Research Fund
Kean et al. (2017)	Conners Parent Rating Scales (CPRS)	Test of Variables of Attention and Computerised Mental Performance Assessment	The results did not indicate any correlation between treatment group and CPRS measures; however,	Participants in the intervention groups demonstrated improved memory in cognitive tasks,	Variety in participant demographics	Pharmalink Pty Ltd. (industry)

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Table 6. (continued)

		System as the secondary outcome variables to assess cognition and hyperactivity/attention symptoms	subgroup analysis showed that participants with non-combined type participants with less severe symptoms showed improved CPRS hyperactivity scores, as well as those on behavior at home and learning abilities	indicating the potential benefit of *n*-3 supplementation on delayed working memory in particular		
Keim et al. (2018)	Bayley-III composite score	The Bayley-III language and motor composite scores and the IBQ-R and Early Childhood Behavior Questionnaire effortful control and activity level scores	The results did not indicate improvement on the basis of daily DHA and AA supplementation for this population	In all but the poorest groups and those with the lowest birth weight, some negative effects in early language ability were identified, suggesting that those children may not have been previously deficient in DHA/AA and the supplementation therefore upset their previous fatty acid balance in the brain	Smaller than planned sample size; underpowered to detect subgroup differences	US Health Resources and Services Administration Maternal and Child Health Field–initiated Innovative Research Studies Program; the March of Dimes, the Allen Foundation; Cures Within Reach; National Center for Advancing Translational Sciences/ National Institutes of Health; Research Institute at Nationwide Children's Hospital
Kim et al. (2010)	Academic grades		Participants who reported fish consumption more than once per week reported higher grades than those with lower levels of fish consumption	Fish consumption may correlate with higher academic achievement	Lack of more detailed dietary information	Swedish Society of Medicine, the Department of Public Health at the Västra Götaland Region
Kennedy et al. (2009)	Internet Battery; Cognitive Drug Research (CDR) Battery		Those in the 400 mg DHA group performed better on the word recognition task, while those in the higher dosage group performed more slowly	The authors suggested that this findings was likely due to chance	Sample size; slight lack of power	Martek Biosciences
Kirby et al. (2010)	Kaufman Brief Intelligence Test, Wechsler Individual Achievement Test Working Memory Test Battery for Children, Creature Counting for attention, the Matching Familiar Figures Task (MFFT), the Computerised Penmanship Evaluation Tool, the SNAP-IV ADHD rating scale, and the SDQ		On the MFFT (which measures impulsivity and visual perception), the supplemented group had a significantly higher number of first correct responses than the control group. The placebo group also demonstrated lower levels of parent-reported prosocial behavior	Supplementation could have had a protective effect against decline in prosocial functioning	Longer supplementation period may have been necessary; while statistically significant, correlations identified were weak	Seven Seas Ltd (supplement production)
Mazahery et al. (2019)	Social responsiveness scale (SRS) and sensory processing measure (SPM)	Biochemical analysis	Of the four social functioning domains assessed in the SRS, improved social awareness was found to be significantly correlated with both the *n*-3 and *n*-3 + vitamin D interventions. The SPM results indicate possible correlations between the taste and smell domain with *n*-3 +	Noting that other studies have speculated on the benefit of *n*-3 and vitamin D supplementation in combination, given that they have shared/ complementary nutrient functions, the authors noted this type of combined treatment to have a nonsignificant positive effect on social	Smaller than anticipated sample size	Massey University Strategic Innovation Fund, Massey University, New Zealand

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			vitamin D supplementation and between the balance and motion domain with *n*-3 supplementation	interaction and communication		
Milte et al. (2012)	Wechsler Individual Achievement Test III (literacy); Conners Rating Scales (behavior)	Test of Everyday Attention for Children; computerized go/no-go task	DHA proportion was associated with improved scores on word reading measures and lower parent-rated oppositional behavior; DHA level associated with improved reading, spelling, ability to divide attention, parent-ratted oppositional behavior, hyperactivity, restlessness, and ADHD symptoms	Among children with ADHD, LC PUFA supplementation can improve literacy and behavior outcome measures	Smaller than intended sample size; not all children had a clinical ADHD diagnosis	South Australian Health Department; Australian Research Council Linkage Project; Novasel Australia
Milte et al. (2015)	Wechsler Individual Achievement Test–III and the Wechsler Scale of Children's Intelligence–III for the primary outcome measures of literacy and behavior	A test battery from the TEA-ch was used to assess for attention and inhibition behaviors as a secondary outcome measure compared with erythrocyte PUFA status	Increased erythrocyte levels of EPA, DHA, and *n*-3 FAs overall (resulting in lower *n*-6 to *n*-3 ratios) correlated with improved overall literacy, attention, and parent-rated behavior measures	Contrary to previous findings on the importance of EPA over DH, results indicate DHA as an important factor in the positive results observed in this study	Small sample size	Australian Research Council Linkage Grant; Novasel Australia (industry)
Montgomery et al. (2013)	British Ability Scales (II); Connors' rating scales		Lower levels of DHA were found to correspond to lower reading levels and inferior working memory performance; higher levels of oppositional behavior and emotional liability	The authors suggested that DHA supplementation may be particularly useful for children with learning differences	Other nutritional ingredients/components of fish may have produced the positive results; further study is required	Martek Biosciences
Øyen et al. (2018)	Wechsler Pre-school and Primary Scale of Intelligence, 3rd edition (WPPSI-III) and the 9-Hole Peg Test (9-HPT)	Biological samples and caregiver questionnaires	Overall, there were no differences between the groups on the WPPSI-III, and a slightly better improvement, with the non-dominant hand, on the 9-HPT for the fish group. However, when researchers adjusted for dietary compliance, the WPPSI-III total raw score improved more in the fish than the control group: more specifically, fatty fish intake correlated with the Vocabulary, Block Design, and Symbol Search subtests of the outcome measure	Red blood cell DHA concentration was found to be a mediating factor for the WPPSI-III total raw score	Smaller than expected sample size; a longer intervention period may have yielded different results	The Norwegian Seafood Research Fund
Parletta et al. (2013)	(Draw-A-Person) non-verbal cognitive development; reading; and spelling	Conners Behaviour Rating Scales (completed by teachers)	Improvements in Draw-A-Person scores in treatment group, and in placebo group after switching to treatment	The intervention appeared to produce improvements in cognitive development, but not literacy	Low dosage; longer intervention may have produced more effects	Australian Research Council; Vifor Pharma
Portillo-Reyes et al. (2014)	Neuropsychological test battery	Anthropometric and academic measures; parent-completed food frequency questionnaire	Among more than 70% of malnourished children in the treatment group, improvements were seen in processing speed;	Clinically significant cognitive improvements of 3 months of supplementation among malnourished children	Homogenous group in terms of SES; serum and *n*-3 to *n*-6 ratios not assessed	n/s

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Table 6. (continued)

			perceptual integration; visual-motor coordination; attention; executive function			
Raz et al. (2009)	Conners' Abbreviated Parent-Teacher questionnaire; DSM-IV questionnaire for ADHD; Continuous Performance Test	Blood tests; EFA deficiency questionnaire	Both the EFA and the 1000 mg vitamin C placebo appeared to improve ADHD symptoms	EFA supplementation does not appear to work beyond a placebo effect on improving ADHD symptoms	EFA amount or composition may have been less than optimal	No disclosures reported
Richardson and Montgomery (2005)	Movement Assessment Battery for Children; Wechsler Objective Reading Dimensions; Conners' Teacher Rating Scales, Long Version		No effect on motor skills; significant improvements to reading, spelling, and behavior scores	FA supplementation may function as a treatment option for DCD	Optimal dosage information unknown; more studies required	Dyslexia Research Trust; Durham Local Education Authority
Richardson et al. (2012)	Reading; working memory; parent- and teacher-rated behavior		No effect of supplementation on reading for the group overall; a subgroup of more significantly underperforming students showed significant reading improvements; parent-rated behavior improved	DHA supplementation offers potential for improvements to reading, particularly among severely underperforming children	Missing data from parent ratings may have caused positive bias	Martek Biosciences
Ryan and Nelson (2008)	Leiter-R Test of Sustained Attention, Peabody Picture Vocabulary Test (PPVT), Day-Night Stroop Test, and Conners' Kiddie Continuous Performance Test	Interaction between blood DHA levels and efficacy end points	While the results did not indicate significant treatment effects on the primary outcome measures, regression analysis did indicate a significant positive correlation between DHA level and higher PPVT scores	Since the PPVT tests for comprehension in English, and is associated with memory and cognitive function, these results suggest potential implications in those domains in particular	Ceiling effect reduced the sample size	n/s
Sheppard and Cheatham (2013)	Cambridge Neuropsychological Test Assessment Battery (specifically focused on executive function and working memory)	Spatial Working Memory (SWM); Spatial Span (SSP); Stockings of Cambridge (SOC); Intra-Extra Dimensional Set Shift	Participants with balanced *n*-6 to *n*-3 ratios demonstrated shorter initial processing times on the spatial working memory task, shorter mean planning times on the planning task, and better executive function scores overall	Balanced intake of *n*-3 and *n*-6 fatty acids is important, as when *n*-3 and *n*-6 intake were both low (low ratio) and when *n*-3 intake was high and *n*-6 intake was very high (high ratio), results were good	Small but sufficiently powered sample size; results require replication; only spatial memory tests included in this study	North Carolina Translational and Clinical Science Institute
Sinn et al. (2008)	ADHD-related symptoms on Conners' Parent Rating Scales (CPRS)—Revised; cognitive test battery		Significant improvements in ability to shift and control attention among the supplementation group	Supplementation may yield minor improvements for this population	Not possible to detect meaningful cognitive outcomes on all tests; lack of intention-to-treat analysis	University of South Australia; Commonwealth Scientific and Industrial Research Organisation
Sørensen et al. (2015)	d2-test of attention and Danish standard tests in reading and maths	Physical activity; dietary intake; biomarkers of PUFA status	Overall school performance, reading comprehension and blood EPA + DHA levels improved as a result of the intervention	Dietarily derived *n*-3 LC PUFAs have positive cognitive effects on school-aged children	No participant blinding; short study period	Nordea Foundation
Widenhorn-Müller et al. (2014)	Cognitive assessment: Hamburg Wechsler Intelligence Scales for	Behavior assessment: FBB ADHS parent-rated and teacher-rated	While scores for parent-rated (DISYPS-II, CBCL) and teacher-rated	The authors suggested that the working memory improvement may be	Small sample size; inability to determine whether the working	German Federal Ministry of Education and Research

(continued)

Table 6. (continued)

	Children–IV (particularly working memory and processing speed domains); "Test-batterie zur Aufmerksamkeitsprüfung für Kinder" (KITAP 6–10 y) and the "Testbatterie zur Aufmerksamkeitsprüfung" (TAP 10-18y) for attentional performance	questionnaires; Child Behavior Checklist 4–18 y; Teacher's Report Form 5-18 y	(DISYPS-II, TRF) behavior did not change significantly, there was a significant improvement in working memory among the intervention group; there was a significant decrease of parent-rated thought problems in the placebo group, which may have been caused by the oleic acid in the placebo capsules	specific to a population with ADHD, but that future research is required to determine this	memory finding was specific to children with ADHD	
van der Wurff et al. (2016)	Letter Digit Substitution Test (LDST), D2 test of attention, Digit Span Forward and Backward, Concept Shifting Test, and Stroop test	Questionnaires to assess covariates and fish consumption	On the LDST, results indicate that a higher omega-3 index was associated with better information processing speeds: each 1% higher the omega-3 index, the LDST score improved by 1.23 digits. On the D2 test of attention, participants with higher omega-3 levels had fewer errors of omission, which indicates less impulsivity	Overall, the results indicate a positive effect of omega-3 supplementation on select cognitive measures	Observational study; cannot prove causality	Food, Cognition and Behaviour from the Dutch Scientific Organisation
van der Wurff et al. (2019)	Letter digit substitution task (LDST), the D2 test of attention (D2), and the Digit Span backward and forward. After these group tests were administered, the Stroop Interference Test and the Concept Shifting Task were administered individually	Pubertal Development Scale; demographic questionnaires	The results did not indicate an effect of one year of krill oil supplementation on participants, or between O3I and neurocognitive test scores	However the authors noted a high level of non-compliance, and suggested that adherence difficulties may have contributed to the lack of demonstrated correlation between krill oil supplementation and neurocognitive benefits	High drop-out rate; low adherence	The Netherlands Organization for Scientific Research; AkerBiomarine (fishing and biotech with krill interests)
Vesco et al. (2018)	Behavior Rating Inventory of Executive Functioning (BRIEF)	Mood disorders and mood symptom severity assessed using K-SADS Depression (KDRS) and Mania Rating Scales (KMRS) (Geller et al., 2001), the Children's Depression Rating Scale-Revised (CDRS-R), and Young Mania Rating Scale (YMRS)	Both intervention groups receiving *n*-3 supplementation (with and without PEP), showed a significant improvement in executive functioning, particularly in the areas of inhibition control, adaptability to emotions, and cognitive flexibility	The authors noted that, while this study indicates a potentially positive effect of *n*-3 supplementation on executive functioning treatment for mood disorders, further research should be conducted to assess for ideal supplementation amounts and to identify moderating effects	Potential parental bias on symptom ratings; short-term nature of follow-up; uncertainty as to whether results generalize to populations without mood disorders	National Institute of Mental Health; National Center for Research Resources
Voigt et al. (2001)	Test of Variables of Attention and Children's Color Trails test (inattention measures); Child Behavior Checklist, Conners' Rating Scale (parent-rated behavior scales	Plasma phospholipid DHA content	No statistically significant effect of supplementation on ADHD among this population	The treatment intervention did not appear to be efficacious in improving inattention or parent-rated behavior related to ADHD	Plasma phospholipid DHA content may not indicate DHA presence in brain or synapses	US Department of Agriculture; Martek Biosciences Corporation

cognitive performance after intervention. Sheppard and Cheatham also addressed food-derived *n*-3s (specifically in relation to *n*-6: *n*-3 ratios) in terms of effect on cognitive function through an observational study using diet recalls and histories rather than a supplement intervention, and found that participants with balanced ratio scores scored higher on overall measures of executive function.[66] Importantly, the results indicate that when intake for both n-3 and n-6 was high (low ratio) cognitive abilities declined. In comparison to other studies, these results are important due to the focus on balance rather than high levels of supplementation, and may interact with/help explain the threshold findings offered in other studies.

Particularly among adolescents, compliance issues may introduce biases in studies that address these populations. Handeland et al. also found that, while dietary intake is preferable to supplementation, taste preferences may be a factor.[67] The results of the study by van der Wurff et al. did not indicate an effect of 1 year of krill oil supplementation on participants, or between n-3 index and neurocognitive test scores.[68] However, the authors noted a high level of non-compliance, and suggested that adherence difficulties may have contributed to the lack of a demonstrated correlation between krill oil supplementation and neurocognitive benefits.

Specific Outcomes of Interest. Given the prefrontal cortex development that occurs in childhood and adolescence, and the increasing ability to test for higher-order cognitive functions among older children, studies conducted during the later childhood and adolescence period in particular assessed for higher-order cognitive function, including: attention and executive functioning, information processing speeds and impulsivity, and memory.

Attention and Executive Functioning. Several studies found that DHA supplementation can have positive effects on attention and executive functioning during the childhood and adolescence periods, in both clinical and cognitive healthy populations. For instance, Vesco et al. studied a group of 7-14-year-olds with disorders that affect executive functioning, and found that n-3 supplementation may aid in executive functioning treatment for mood disorders.[69] In particular, executive functioning in the areas of inhibition control, adaptability to emotions, and cognitive flexibility improved more than in the areas of task initiation, planning, and organization. In the FINS-TEENS study, Handeland et al. found that total performance and processing speed improved in the fish meal group compared to meat and supplement groups; the authors noted that dietary intake appears preferable to supplementation.[67]

Information Processing Speeds and Impulsivity. Van der Wurff et al. found that, on a letter digit substitution test, a higher omega-3 index was associated with better information processing speeds: each 1% higher the omega-3 index, the LDST score improved by 1.23 digits.[70] On the D2 test of attention, participants with higher omega-3 levels had fewer errors of omission, which indicates less impulsivity. While the overall results did not indicate an impact of fatty fish intake on general cognitive function, Øyen et al. did report a small beneficial effect on three subtests: processing speed subscale, coding and symbol search, and non-dominant hand 9-HPT, with 78% power to detect an effect size of .37.[65] Due to DHA's role in neural communication, the dietary increases to n-3 intake in this study may indicate an interaction with processing speed, though the results are inconclusive and further studies using processing speed measures are indicated. Other studies have also reported an interaction between LC PUFAs and measures of impulsivity, primarily among the adolescent population. One study with a younger population (8-10 years of age) included the Matching Familiar Figures Test (MFFT) to measure visual attention and impulsivity, and found that the number of first correct responses increased with supplementation, although the study overall did not yield positive results.[64]

Memory. Ryan and Nelson found that, while their results did not indicate significant treatment effects on the primary outcome measures, regression analysis did indicate a significant positive correlation between DHA level and higher PPVT scores (which tests for listening comprehension in English, and is associated with memory and cognitive function).[71] Sheppard and Cheatham similarly found a balanced n-3: n: 6 ratio correlated with better working memory scores.[66] Widenhorn-Müller et al. found DHA/EPA supplementation to improve working memory among a population with ADHD.[72]

Cognitively Clinical Populations Studies

During the childhood and adolescence supplementation period, an increasing number of studies have addressed clinical rather than typically developing populations, assessing for the effect of LC PUFAs on pathologies including ADHD and ASD.

ADHD. Given the high concentration of DHA in the frontal areas of the brain associated with executive function, the correlation between n-3s and ADHD symptomatology have been of interest to various researchers. Crippa et al. tested the effect of DHA as an ADHD monotherapy.[73] The results showed no difference between treatment and intervention group on the primary outcome measure: ADHD rating scale IV. However, DHA supplementation did appear to produce small benefits to focused attention, parent-rated improvements to psychosocial functioning, and parent-identified reductions in emotional problems.

Raz et al. did not find supplementation with EFA to produce any amelioration of ADHD symptoms beyond that of the placebo effect.[74]

Kean et al. reported improved Conners' Parent Rating Scale, behavior at home, and learning abilities scores as a result of supplementation with green-lipped mussel extract.[75] Further, participants in the intervention groups demonstrated improved memory in cognitive tasks, indicating the potential benefit of *n*-3 supplementation on delayed working memory in particular. Similarly, Milte et al. supplemented children with EPA, DHA, or linoleic acid for 4 months, and although outcome measures showed no significant differences between the three treatments, the Authors found that increased erythrocyte levels of EPA, DHA, and *n*-3 FAs overall (resulting in lower *n*-6 to *n*-3 ratios) correlated with improved overall literacy, attention, and parent-rated behavior measures.[76,77]

ASD. Due to insufficiencies of pharmacological treatments, there has been increasing interest in complementary and supplement-based treatments for ASD, including *n*-3 LC PUFAs, DHA and EPA.[78] 1 study evaluating the efficacy of vitamin D, LC PUFA, or both, on core symptoms of ASD reported that improved social awareness and social communicative functioning was significantly correlated with both *n*-3 and *n*-3 + Vitamin D interventions. Authors suggested that either alone or in combination with Vitamin D, *n*-3s can have a positive effect on the core symptoms of ASD.[79]

Discussion

This review evaluated the effect of omega-3 fatty acid supplementation on neurodevelopment in 3 different cognitive developmental phases: *in-utero*; lactation/infancy; and childhood and adolescence. Overall, the clinical studies reviewed reported equivocal results regarding cognitive function among the 3 populations.

Generally, researchers have reported beneficial effects on several specific cognitive domains, and at times with small effect sizes. The most consistent positive results include those pertaining to language/communication, executive functioning, attention, and memory.

Further, most research is conducted among populations that do not exhibit deficiencies in *n*-3 LC PUFA status, and numerous studies indicate the presence of a threshold or even a U-shaped curve in relation to *n*-3 consumption. It could appear that in populations that are not deficient in DHA or other *n*-3 LC PUFAs, supplementation has a negligible or at times detrimental effect. Few studies have addressed populations that are deficient in *n*-3s; 1 study conducted on a population of children with mild to moderate malnourishment resulted in improvements in an extensive number of domains on a neuropsychological test battery.[80]

Although LC PUFAs supplied during infancy and *in-utero* seldom have shown significant cognitive effects, it appears that they do not persist at long-term follow-up assessments. This may indicate that other confounding variables such as nutritional and lifestyle factors can influence the outcomes in the intervening years. In dietary-based studies in particular, authors noted that higher levels of fish intake tend to correlate with higher parental education and socioeconomic status levels, which may confer their own benefits. However, while most studies have alluded to the superiority of dietarily-derived omega-3 sources, a recent study found no effect of supplementation with fatty fish or rapeseed oil from 5-10 months post-delivery on infants' latencies of FVEP, Bayley's MDI, or in PDI index.[48]

Several studies across intervention periods yielded gender-dependent results, but further research on differences in how *n*-3 LC PUFAs are metabolized and synthesized according to sex is required to draw clear conclusions.

Overall, the authors of the majority of the studies with short interventions noted that it is important for *n*-3s to be supplied throughout life, rather than only during the earliest developmental stages.

The main strength of this systematic review is the fairly large number of papers analyzed and searched through multiple databases. Including reference lists in the search assured a comprehensive overview of the published studies. Also, To avoid bias, manuscripts were reviewed by two reviewers.

This review has also several limitations. Inconsistencies in LC PUFA source and type persist across the included studies, and contribute to the equivocality of the overall results. Studies have tested DHA in isolation, or in combination with EPA, ARA, and AA, derived from different sources and administered in a broad range of dosages. Further, some researchers have addressed an advantage of dietarily derived over supplement based *n*-3s, which may be due to bioavailability. For instance, LC PUFAs in fatty fish are bound to both phospholipids and triacylglycerol, whereas those in supplements are only bound to triacylglycerol.[67] Another source of bias could be that nearly all studies, even those funded by purely academic or governmental sources, reported that the intervention capsules/supplements were provided by a supplement or vitamin industry stakeholder.

Conclusion

Studies addressing *n*-3 LC PUFA supplementation at three key neurodevelopmental periods—*in-utero*, during the first year of life, and throughout childhood and adolescence—have reported some benefits in the areas of visual attention, working memory, executive function, and communication. However, effects are more often reported for specific cognitive domains rather than cognitive composite scores and do not tend to persist to long-term follow-up assessment. This may be due in part to the presence of confounding variables like other demographic and lifestyle characteristics and methodological difficulties (like lack of compliance, loss to follow-up, and a very broad range of outcome measures, dosages, and intervention types). Findings remain equivocal, and further research that is powered to detect small, subgroup effect sizes remains necessary.

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