GLOBAL ORGANIZATION FOR EPA AND DHA OMEGA-3S

18 December 2024

Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality
ATTN: EPC SEADs Coordinator
5600 Fishers Lane, Mail Stop 06E53A
Rockville, MD 20857
epc@ahrq.hhs.gov

RE: Request for Supplemental Evidence and Data (SEAD) Submission for *Dietary Total Fat Intake and Dietary Polyunsaturated Fatty Acid Intake and Child Growth and Development Outcomes: A Systematic Review*

Dear EPC SEADs Coordinator:

GOED, the Global Organization for EPA and DHA Omega-3s, represents the worldwide EPA and DHA omega-3 industry, with a membership built on a quality standard unparalleled in the market. Members must comply with quality and ethics guidelines that ensure they produce quality products that consumers can trust. Our 200+ members and partners represent the entire supply chain of EPA and DHA omega-3s, from fisheries and crude oil suppliers to refiners, concentrators and finished product brands. Our mission is to use science-based information to promote consumption of and enable access to quality EPA & DHA from all sources for a positive impact on public health.

Given our mission, we appreciate the opportunity to provide comments (i.e. supplemental evidence and data (SEAD)) on the research protocol for *Dietary Total Fat Intake and Dietary Polyunsaturated Fatty Acid Intake and Child Growth and Development Outcomes: A Systematic Review*.[1] We will focus on EPA and DHA as it relates to the key questions, and we are not addressing total fat intake (Question #3), omega-6 intake or the ratio of different fatty acids. In addition, while your request is specific to providing supplemental evidence and data on the research protocol, we have provided some commentary to put the evidence into context.

Question #1

- What is the association between dietary intake of omega-6 and/or **omega-3 polyunsaturated fatty acids** during pregnancy and risk of preterm birth?
  a. How are these associations affected by intervention/exposure characteristics (for example, the ratio of different fatty acids)?

Of the four key questions, Question #1 has the largest, not to mention strongest, body of supporting scientific evidence. We are not providing a specific list of publications to consider,

[1] https://effectivehealthcare.ahrq.gov/products/child-growth-development-outcomes/protocol

but referring you to a 2018 Cochrane review,[2] which included an exhaustive literature review on the effects of EPA & DHA during pregnancy on the risk of preterm and early preterm birth. Its reference list includes many interventional studies for consideration regarding your systematic review.

According to this Cochrane review, preterm birth (< 37 weeks) and early preterm birth (< 34 weeks) were reduced in women receiving EPA & DHA compared with no EPA & DHA.

- Preterm birth: 13.4% in the EPA & DHA group compared to11.9% in the placebo group; risk ratio (RR) 0.89, 95% confidence interval (CI) 0.81 to 0.97; this data was compiled from 26 RCTs, 10,304 participants; rated as high-quality evidence
- Early preterm birth: 4.6% in the EPA & DHA group compared to 2.7% in the placebo group; RR 0.58, 95% CI 0.44 to 0.77; this data was compiled from 9 RCTs, 5,204 participants; rated as high-quality evidence

Importantly, the authors concluded the following:

> *Omega-3 LCPUFA supplementation during pregnancy is an effective strategy for reducing the incidence of preterm birth, … More studies comparing omega-3 LCPUFA and placebo (to establish causality in relation to preterm birth) are not needed at this stage. A further 23 ongoing trials are still to report on over 5,000 women, so no more RCTs are needed that compare omega-3 LCPUFA against placebo or no intervention.*

Since the publication of the Cochrane Review, which we understand is in the process of being updated, several noteworthy papers have been published that provide additional insight into the benefits of EPA & DHA intake during pregnancy for reducing the risk of preterm and early preterm birth.

In 2022, the International Society for the Study of Fatty Acids and Lipids (ISSFAL) published a position statement on omega-3 fatty acids (EPA & DHA) during pregnancy to reduce preterm birth.[3] Among the information relevant to the current AHRQ review is the following:

> *The statement contains evidence from the Cochrane Review of 'Omega-3 Addition in Pregnancy' published in 2018. In addition, supplemental evidence from RCTs completed since this time as well as other systematic reviews of relevant investigations have been*

[2] Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. Cochrane Database Syst Rev. 2018 Nov 15;11(11):CD003402. doi: 10.1002/14651858.CD003402.pub3. PMID: 30480773; PMCID: PMC6516961.
https://pubmed.ncbi.nlm.nih.gov/30480773/

[3] Best KP, Gibson RA, Makrides M. ISSFAL statement number 7 - Omega-3 fatty acids during pregnancy to reduce preterm birth. Prostaglandins Leukot Essent Fatty Acids. 2022 Nov;186:102495. doi: 10.1016/j.plefa.2022.102495. Epub 2022 Sep 30. PMID: 36228573.
https://www.plefa.com/article/S0952-3278(22)00107-7/fulltext

incorporated. We focused our attention on the results of RCTs with omega-3 LCPUFA intervention/s vs control in conjunction with a grading of quality, because this most often leads to "trusted" guidance. RCTs published to August 2021 are included." Among the implications for policy and practice include, "Adequate intake of omega-3 LCPUFA in early pregnancy, consistent with existing nutritional guidelines, is associated with a lower risk in preterm and early preterm births…

Further evidence of the overwhelming benefits of providing EPA & DHA during pregnancy for reducing the risk of preterm and early preterm birth can be found in a clinical practice guideline[4] on behalf of Asia Pacific Health Association (Pediatric-Neonatology Branch), Child Health Foundation (Stiftung Kindergesundheit), European Academy of Paediatrics, European Board & College of Obstetrics and Gynaecology, European Foundation for the Care of Newborn Infants, European Society for Paediatric Research, and International Society for Developmental Origins of Health and Disease, as well as in a position statement[5] by the European Board and College of Obstetrics and Gynaecology (EBCOG).

Finally, it's worth noting that in 2021, the Australian Pregnancy Care Guidelines[6] were updated to include advice to supplement with EPA & DHA in order to reduce the risk of preterm birth. Australia's guideline, as a case study of translating the results from omega-3 research into practical guidance, can be reviewed by clicking here.

Questions #2 & #4

- What is the association between dietary intake of omega-6 and/or **omega-3 polyunsaturated fatty acids** during pregnancy and/or lactation and infant/child growth and developmental outcomes?
  a. How are these associations affected by intervention/exposure characteristics (for example, the ratio of different fatty acids)?

[4] Cetin I, Carlson SE, Burden C, da Fonseca EB, di Renzo GC, Hadjipanayis A, Harris WS, Kumar KR, Olsen SF, Mader S, McAuliffe FM, Muhlhausler B, Oken E, Poon LC, Poston L, Ramakrishnan U, Roehr CC, Savona-Ventura C, Smuts CM, Sotiriadis A, Su KP, Tribe RM, Vannice G, Koletzko B; Clinical Practice Guideline on behalf of Asia Pacific Health Association (Pediatric-Neonatology Branch), Child Health Foundation (Stiftung Kindergesundheit), European Academy of Paediatrics, European Board & College of Obstetrics and Gynaecology, European Foundation for the Care of Newborn Infants, European Society for Paediatric Research, and International Society for Developmental Origins of Health and Disease. Omega-3 fatty acid supply in pregnancy for risk reduction of preterm and early preterm birth. Am J Obstet Gynecol MFM. 2024 Feb;6(2):101251. doi: 10.1016/j.ajogmf.2023.101251. Epub 2023 Dec 7. PMID: 38070679.
https://www.ajogmfm.org/article/S2589-9333(23)00393-2/fulltext

[5] Savona-Ventura C, Mahmood T, Mukhopadhyay S, Louwen F. Omega-3 fatty acid supply in pregnancy for risk reduction of preterm and early preterm birth: A position statement by the European Board and College of Obstetrics and Gynaecology (EBCOG). Eur J Obstet Gynecol Reprod Biol. 2024 Apr;295:124-125. doi: 10.1016/j.ejogrb.2024.02.009. Epub 2024 Feb 6. PMID: 38354604.
https://pubmed.ncbi.nlm.nih.gov/38354604/

[6] https://app.magicapp.org/?language=en#/guideline/jm83RE

- What is the association between dietary intake of omega-6 and/or **omega-3 polyunsaturated fatty acids** in individuals birth through 18 years of age and measures of growth and development?

Generation of Study Lists:
To provide a list of references relevant to the topics of growth and development, GOED relied on an internal research tool, the Clinical Study Database (CSD),[7] launched in 2022. This novel tool, designed to enhance our ability to search for and utilize the research on EPA & DHA, catalogs the relevant information contained in articles indexed by PubMed.

As a further explanation of the CSD functionality, each article in PubMed potentially about EPA and/or DHA is imported into the CSD, where it is reviewed by two scientists, and a third in case of disagreement. The results of this review (99% finished as of Nov, 2024 – a lag time in PubMed assigning and reviewing MeSH (Medical Subject Headings) terms makes it impossible to surpass that level of completeness) can be used to create carefully curated lists of studies, with reasonable certainty they will be about EPA and/or DHA, and they are of the required study type.

The CSD allows users to identify all interventional trials whose intervention includes EPA and/or DHA, and for these articles a more extensive data extraction is done, including participant number and baseline characteristics, interventions and placebos, and the outcomes measured.

A typical PubMed (or similar) search allows users to look for keywords defined by the article authors or by the PubMed system. However, this method of searching doesn't allow for the retrieval of studies that measured an outcome but did not list it as a key word. Most outcomes reported on a paper never make it into the MeSH term list (the controlled vocabulary behind both PubMed and the CSD) or are not mentioned in the abstract. The CSD makes it possible to search interventional studies for all outcomes measured, and not merely for words in the title or abstract. A useful example is blood pressure. While many/most clinical trials measure blood pressure, this is seldom the study's focus and is rarely mentioned as a keyword or in the results listed in the Abstract. Even if blood pressure is not included as a keyword, using the CSD, we can see all studies that measured blood pressure, independent of whether it was an author-defined or search-engine defined outcome.

Given the importance of this project, we have used the CSD to compile supporting lists of references for the AHRQ request for publications related to omega-3 polyunsaturated fatty acids and "growth and development." In order to generate this list of references, we used the AHRQ defined terms for growth and development as a starting point. To elaborate, we reviewed the Cochrane review[2] for terms of importance. Then we cross referenced the AHRQ terms and the

[7] Bernasconi AA, Wilkin AM, Roke K, Ismail A. Development of a novel database to review and assess the clinical effects of EPA and DHA omega-3 fatty acids. Prostaglandins Leukot Essent Fatty Acids. 2022 Aug;183:102458. doi: 10.1016/j.plefa.2022.102458. Epub 2022 Jun 23. PMID: 35816925. https://pubmed.ncbi.nlm.nih.gov/35816925/

Cochrane review terms for the connected terms within the CSD. In Tables 1 and 2, you'll find the AHRQ terms for growth (Table 1) and development (Table 2), the Cochrane Review terms for developmental outcomes (Table 2) and the CSD terms for growth (Table 1) and development (Table 2).

Table 1: Infant and Child (birth through 18 years) Growth Outcomes (from AHRQ) and Associated Terms from the GOED CSD

AHRQ Growth Terms	CSD Growth Terms
Birth weight	• Birth Weight • Birth Weight for Age • Birth Weight for Length • Infant, Extremely Low Birth Weight • Infant, High Birth Weight • Infant, Low Birth Weight • Infant, Low Birth Weight, <2000g • Infant, Very Low Birth Weight
Weight and Weight-for-age percentile or Z-score adjusted for gestational age	• Birth weight, z-score • Birth Weight for Length, z-score • Birth Weight, <25 Percentile • Birth Weight, <50 Percentile • Birth Weight, <75 Percentile • Weight velocity
Length or Height and Length-for-age or Height-for-age percentile and Z-score adjusted for gestational age	• Birth Length • Birth Length, z-score • Body Height • Body Height Growth Rate • Body Height, z-score

Head circumference and Head circumference percentile and Z-score adjusted for gestational age	• Head circumference • Head circumference, z-score • Head Circumference Growth Rate

Table 2: Infant and Child (birth through 18 years) Developmental Outcomes (from AHRQ), from Middleton et al (Cochrane review) and Associated Terms from the GOED CSD

AHRQ Development Terms	**Middleton Development Terms**	**CSD Terms**
Cognitive / neurological	<u>Child Development Inventory</u> <u>Neurodevelopment (overall): thresholds</u> • Hempel: simple minor neurological dysfunction • Hempel: simple and complex minor neurological dysfunction • Hempel: complex minor neurological dysfunction • Ages & Stages Questionnaire (ASQ); ASQ total • Neonatal neurological classification: mildly/definitely abnormal • General movements: mildly/definitely abnormal	• Child Development • Neurodevelopment, Subnormal • Neurodevelopmental Disorders • Neurologic Examination • Ages and Stages Questionnaire, *and all associated outcomes* • Kaufman Assessment Battery for Children, *and all associated outcomes* • Neuropsychological Test Battery, *and all associated outcomes*
	<u>Behaviour: scores</u> • Neonatal Behaviour Assessment Scale (NBAS)	• Vineland Adaptive Behavior Scales, *and all associated outcomes*

	habituation, orienting, motor, state organization, autonomic, reflexes • Behavior Rating Scale • Wolke: approach, activity, co-operation, emotional tone, vocalization • BSID III • Strengths and Difficulties Questionnaire (SDQ) Total Difficulties • Behavioral Symptoms Index Composite Score (BASC-2) • Child Behaviour Checklist (CBCL) <u>Cognition: thresholds</u> • Bayley Scales of Infant Development (BSID) II or III	• Attention Network Test, *and all associated outcomes* • Attention, Orienting • Behavior Rating Scale • Habituation, Psychophysiologic • Attention, Looks to Habituation • Behavior Assessment Scale for Children • Strengths and Difficulties Questionnaire, *and all associated outcomes* • Child Behavior • Child Behavior Checklist, *and all associated outcomes* • BSITD, *and all associated outcome assessments* • Bayley Scales for Infant and Toddler Development • BASC, Parent Rating Scale • BASC, Teacher Rating Scale
	<u>Cognition: scores</u> • BSID II or III • Fagan novelty preference • Kaufman Assessment Battery for Children (K-ABC)	• DASS, Anxiety Score • DASS, Depression Score • DASS, Stress Scale • Wechsler Scales

	• Griffith Mental Development Scale (GMDS) • Differential Ability Scales (DAS) II • Wechsler Abbreviated Scale of Intelligence (WASI) full-scale intelligence quotient (IQ) • Wechsler Intelligence Scale for Children (WISC) IV full scale IQ • MCDS: scale index general cognitive	• Wechsler Intelligence Scale, *and all associated outcomes* • Wechsler Memory Scale, *and all associated outcomes* • Wechsler Preschool and Primary Scale of Intelligence Revised, WPPSI-R, Animal Pegs • General Cognitive Functioning • General Cognitive Proficiency • Fagan Test, *and all associated outcome* • Stroop Test, *and all associated outcome assessments*
	<u>Attention: scores</u> • Conners Kiddie Continuous Performance Test Second Edition (K-CPT) • Attention: single-object task, multiple-object task, distractibility (av latency to look when attention focused, global speed (ms), interference (ms), orienting (ms), alertness (ms) • BSID II	• Attention • Attention and Processing Speed, *and all associated outcomes* • Conner's Rating Scales, *and all associated outcomes*

Language / communication	<u>Language: scores</u> • Receptive communication and language (Peabody Picture Vocabulary Test IIIA) • Expressive communication • BSID III • Clinical Evaluation of Language Fundamentals (CELF) Preschool-2 (P2) • Peabody Picture Vocabulary Test <u>Language: thresholds</u> • BSID III • Receptive language • Expressive language • Communicative Development Inventories (CDI) • Non-native constant contrast discrimination <u>Infant Sleep Behavior</u>	• Language Development • Language Tests • Preschool language scale, auditory and expressive • Children's Communication Checklist • CELF, Core Language Score • Peabody Picture Vocabulary Test III • MB-CDI, *and all associated outcomes* • Communication • Vocabulary • Semantic Verbal Fluency Test • Children's Color Trails Test • Digit span, *and all associated outcome assessments*
Movement / physical	<u>Motor: scores</u> <u>Motor: thresholds</u> • BSID II • BSID III	• Motor Skills, Fine • Motor Skills, Fine, Non-Dominant Hand • Movement • Movement Disorders • Touch
Visual function / acuity	<u>Vision: visual acuity (cycles/degree)</u>	• Vision disorders

	Vision: visual evoked potential (VEP) acuity Vision: visual evoked potential (VEP) latency Hearing: brainstem auditory-evoked responses • Latency 1, 3, 5 (ms) • Interpeak latency 1-3, 3-5, 1-5 (ms)	• Vision screening • Vision, Impaired • Vision, Low • Color Vision Defects • Color Vision Defect, Change • Color Vision Defect, Revert to Normal • Visual Acuity, *and all associated outcomes* • Visual Analog Scale • Hooper Visual Organization Test • Memory, Short-Term Visual • Memory, Delayed Visual • Visual Analog Scale
Social / emotional learning		• Social Behavior • Social Participation • Social Responsiveness Scale, *and all associated outcomes* • Social Skills • Social Support • Social Learning • Emotional Intelligence • Emotional Regulation

		• Emotional State Questionnaire • Brief Infant-Toddler Social and Emotional Assessment, BITSEA, *and all associated outcomes* • Clinical Linguistic and Auditory Milestone Scale • RAVLT, *and all associated outcomes* • Reaction Time, *and associated outcomes* • Matching Familiar Figures Task, *and all associated outcomes*

Study Lists in Response to Q2 and Q4

Using the GOED CSD, and the above listed terms, we created eight separate search strings to cover all relevant growth and development outcomes. These eight searches resulted in 937 studies. There were 431 duplicates, which were removed. After studies before 2000 were excluded, there were 463 studies remaining.

Based on this list of 463 studies, the titles of the articles were screened for studies that were more obviously excluded from the AHRQ work. Based on the AHRQ criteria, the titles were scanned to ensure the papers were about pregnant or lactating women, or people between the ages of 0-18 years. Studies with the words “adult” or “patient” were removed, leaving 394 studies. After two scientists reviewed the list, there were 98 further studies in adult populations, and thus those were excluded by both reviewers, leaving 296 studies. Titles without clear populations were passed to a second step where Abstracts were reviewed for relevance. In total, 225 studies remained. These studies are listed in the below tables for consideration for inclusion in this AHRQ review. The studies are broken into four lists. Each of the tables includes studies that fit with different criteria.

All studies included in the lists were evaluated using Population, Intervention, Comparator, Outcome, Timing, Setting/Study Design (PICOTS) in accordance with the AHRQ Methods.

- Population - Pregnant or lactating women, or people between the ages of 0-18 years
    - Participant Health Status - "Healthy" Populations
- Intervention - EPA and/or DHA oral intake (specific to the focus of GOED and this letter)
- Comparator - Varied in each study
- Outcome - Studies including at least one of the above listed growth (Table 1) or development (Table 2) outcomes
- Timing – Varied in each study
- Setting/Study Design - Interventional studies included

Table 3: Studies meeting PICOTS
The following list includes studies with at least one outcome related to growth and/or development. Two scientists reviewed each study, and determined that all studies listed met the PICOTS criteria listed above. **124 Studies Included.**

Year	PMID	Title	PubMed Link
2000	10740336	Randomised clinical trials of fish oil supplementation in high risk pregnancies. Fish Oil Trials In Pregnancy (FOTIP) Team.	https://pubmed.ncbi.nlm.nih.gov/10740336
2000	10755457	A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants.	https://pubmed.ncbi.nlm.nih.gov/10755457
2001	11694666	Similar effects on infants of n-3 and n-6 fatty acids supplementation to pregnant and lactating women.	https://pubmed.ncbi.nlm.nih.gov/11694666
2002	12127385	Supplementation with omega-3 polyunsaturated fatty acids in the management of recurrent migraines in adolescents.	https://pubmed.ncbi.nlm.nih.gov/12127385
2003	12509593	Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age.	https://pubmed.ncbi.nlm.nih.gov/12509593
2003	12532113	Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the Childhood Asthma Prevention Study (CAPS).	https://pubmed.ncbi.nlm.nih.gov/12532113
2003	12636950	A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy.	https://pubmed.ncbi.nlm.nih.gov/12636950

2003	12937042	Maternal docosahexaenoic acid supplementation during pregnancy and visual evoked potential development in term infants: a double blind, prospective, randomised trial.	https://pubmed.ncbi.nlm.nih.gov/12937042
2003	14657879	Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial.	https://pubmed.ncbi.nlm.nih.gov/14657879
2004	15333721	Maturation of visual acuity is accelerated in breast-fed term infants fed baby food containing DHA-enriched egg yolk.	https://pubmed.ncbi.nlm.nih.gov/15333721
2005	15867048	The Oxford-Durham study: a randomized, controlled trial of dietary supplementation with fatty acids in children with developmental coordination disorder.	https://pubmed.ncbi.nlm.nih.gov/15867048
2005	16002810	Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants.	https://pubmed.ncbi.nlm.nih.gov/16002810
2005	16006428	Maternal fish oil supplementation in lactation and growth during the first 2.5 years of life.	https://pubmed.ncbi.nlm.nih.gov/16006428
2005	16188206	Maternal fish oil supplementation in lactation: effect on developmental outcome in breast-fed infants.	https://pubmed.ncbi.nlm.nih.gov/16188206
2006	16702318	Maternal fish oil supplementation during lactation does not affect blood pressure, pulse wave velocity, or heart rate variability in 2.5-y-old children.	https://pubmed.ncbi.nlm.nih.gov/16702318

2007	17240089	Visual acuity and cognitive outcomes at 4 years of age in a double-blind, randomized trial of long-chain polyunsaturated fatty acid-supplemented infant formula.	https://pubmed.ncbi.nlm.nih.gov/17240089
2007	17556695	Maternal consumption of a docosahexaenoic acid-containing functional food during pregnancy: benefit for infant performance on problem-solving but not on recognition memory tasks at age 9 mo.	https://pubmed.ncbi.nlm.nih.gov/17556695
2008	17912568	Soy-based infant formula supplemented with DHA and ARA supports growth and increases circulating levels of these fatty acids in infants.	https://pubmed.ncbi.nlm.nih.gov/17912568
2007	17921387	Effect of a 12-mo micronutrient intervention on learning and memory in well-nourished and marginally nourished school-aged children: 2 parallel, randomized, placebo-controlled studies in Australia and Indonesia.	https://pubmed.ncbi.nlm.nih.gov/17921387
2007	16920077	Omega-3 fatty acids supplementation in children with autism: a double-blind randomized, placebo-controlled pilot study.	https://pubmed.ncbi.nlm.nih.gov/16920077
2008	18326591	Essential n-3 fatty acids in pregnant women and early visual acuity maturation in term infants.	https://pubmed.ncbi.nlm.nih.gov/18326591
2008	18534230	Hypoallergenicity and effects on growth and tolerance of a new amino acid-based formula with docosahexaenoic acid and arachidonic acid.	https://pubmed.ncbi.nlm.nih.gov/18534230

2008	18586645	The effects of docosahexaenoic acid-rich fish oil on behavior, school attendance rate and malaria infection in school children--a double-blind, randomized, placebo-controlled trial in Lampung, Indonesia.	https://pubmed.ncbi.nlm.nih.gov/18586645
2008	18676533	Effect of supplementing pregnant and lactating mothers with n-3 very-long-chain fatty acids on children's IQ and body mass index at 7 years of age.	https://pubmed.ncbi.nlm.nih.gov/18676533
2009	18991979	Do fatty acids help in overcoming reading difficulties? A double-blind, placebo-controlled study of the effects of eicosapentaenoic acid and carnosine supplementation on children with dyslexia.	https://pubmed.ncbi.nlm.nih.gov/18991979
2009	19056592	Docosahexaenoic acid supplementation and time at achievement of gross motor milestones in healthy infants: a randomized, prospective, double-blind, placebo-controlled trial.	https://pubmed.ncbi.nlm.nih.gov/19056592
2009	19091800	Maternal fish oil supplementation during lactation may adversely affect long-term blood pressure, energy intake, and physical activity of 7-year-old boys.	https://pubmed.ncbi.nlm.nih.gov/19091800
2009	19141765	Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/19141765
2009	19156158	Reduced mania and depression in juvenile bipolar disorder associated with long-chain omega-3 polyunsaturated fatty acid supplementation.	https://pubmed.ncbi.nlm.nih.gov/19156158

2009	19174829	The effects of whole milk and infant formula on growth and IGF-I in late infancy.	https://pubmed.ncbi.nlm.nih.gov/19174829
2009	19201180	A randomised control trial in schoolchildren showed improvement in cognitive function after consuming a bread spread, containing fish flour from a marine source.	https://pubmed.ncbi.nlm.nih.gov/19201180
2009	19267292	Early infant diet and the omega 3 fatty acid DHA: effects on resting cardiovascular activity and behavioral development during the first half-year of life.	https://pubmed.ncbi.nlm.nih.gov/19267292
2009	19356306	Cognitive and mood effects of 8 weeks' supplementation with 400 mg or 1000 mg of the omega-3 essential fatty acid docosahexaenoic acid (DHA) in healthy children aged 10-12 years.	https://pubmed.ncbi.nlm.nih.gov/19356306
2009	19369376	Effect of fortification with multiple micronutrients and n-3 fatty acids on growth and cognitive performance in Indian schoolchildren: the CHAMPION (Children's Health and Mental Performance Influenced by Optimal Nutrition) Study.	https://pubmed.ncbi.nlm.nih.gov/19369376
2010	20093894	Omega-3 fatty acid supplementation to prevent recurrent preterm birth: a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/20093894
2010	20171055	A double-blind, placebo-controlled study investigating the effects of omega-3 supplementation in children aged 8-10 years from a mainstream school population.	https://pubmed.ncbi.nlm.nih.gov/20171055

2010	20655543	Effects of early maternal docosahexaenoic acid intake on neuropsychological status and visual acuity at five years of age of breast-fed term infants.	https://pubmed.ncbi.nlm.nih.gov/20655543
2010	20715595	Effects of docosahexaenoic acid supplementation during pregnancy on gestational age and size at birth: randomized, double-blind, placebo-controlled trial in Mexico.	https://pubmed.ncbi.nlm.nih.gov/20715595
2010	20727522	Omega-3 fatty acid supplementation improves vascular function and reduces inflammation in obese adolescents.	https://pubmed.ncbi.nlm.nih.gov/20727522
2010	20959577	Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/20959577
2011	21295417	Cognitive function in 18-month-old term infants of the DIAMOND study: a randomized, controlled clinical trial with multiple dietary levels of docosahexaenoic acid.	https://pubmed.ncbi.nlm.nih.gov/21295417
2011	21490140	Maternal supplementation with docosahexaenoic acid during pregnancy does not affect early visual development in the infant: a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/21490140
2011	21512889	Fish oil supplementation during lactation: effects on cognition and behavior at 7 years of age.	https://pubmed.ncbi.nlm.nih.gov/21512889
2011	21521543	Consumption of a DHA-containing functional food during pregnancy is associated with lower infant ponderal	https://pubmed.ncbi.nlm.nih.gov/21521543

		index and cord plasma insulin concentration.	
2012	22205307	Effect of reducing the n-6:n-3 long-chain PUFA ratio during pregnancy and lactation on infant adipose tissue growth within the first year of life: an open-label randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/22205307
2012	22269042	Maternal consumption of a DHA-containing functional food benefits infant sleep patterning: an early neurodevelopmental measure.	https://pubmed.ncbi.nlm.nih.gov/22269042
2012	22337227	The effects of n-3 long-chain polyunsaturated fatty acids on bone formation and growth factors in adolescent boys.	https://pubmed.ncbi.nlm.nih.gov/22337227
2012	22348468	Effects of high-dose fish oil supplementation during early infancy on neurodevelopment and language: a randomised controlled trial.	https://pubmed.ncbi.nlm.nih.gov/22348468
2012	22739364	Auditory- and visual-evoked potentials in Mexican infants are not affected by maternal supplementation with 400 mg/d docosahexaenoic acid in the second half of pregnancy.	https://pubmed.ncbi.nlm.nih.gov/22739364
2012	22805468	Fish oil supplementation in early infancy modulates developing infant immune responses.	https://pubmed.ncbi.nlm.nih.gov/22805468
2012	22945403	Postnatal fish oil supplementation in high-risk infants to prevent allergy: randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/22945403

2012	22970149	Docosahexaenoic acid for reading, cognition and behavior in children aged 7-9 years: a randomized, controlled trial (the DOLAB Study).	https://pubmed.ncbi.nlm.nih.gov/22970149
2012	23097272	Effects of iron and n-3 fatty acid supplementation, alone and in combination, on cognition in school children: a randomized, double-blind, placebo-controlled intervention in South Africa.	https://pubmed.ncbi.nlm.nih.gov/23097272
2013	23221579	Long-chain PUFA supplementation in rural African infants: a randomized controlled trial of effects on gut integrity, growth, and cognitive development.	https://pubmed.ncbi.nlm.nih.gov/23221579
2013	23426033	DHA supplementation and pregnancy outcomes.	https://pubmed.ncbi.nlm.nih.gov/23426033
2013	23433688	Effects of docosahexaenoic acid supplementation during pregnancy on fetal heart rate and variability: a randomized clinical trial.	https://pubmed.ncbi.nlm.nih.gov/23433688
2013	23756346	Effects of fish oil supplementation on learning and behaviour of children from Australian Indigenous remote community schools: a randomised controlled trial.	https://pubmed.ncbi.nlm.nih.gov/23756346
2013	23783296	Effects of long-chain PUFA supplementation in infant formula on cognitive function in later childhood.	https://pubmed.ncbi.nlm.nih.gov/23783296
2013	23803884	Long-term effects of LCPUFA supplementation on childhood cognitive outcomes.	https://pubmed.ncbi.nlm.nih.gov/23803884

2013	24045099	Fish oil-supplementation from 9 to 12 months of age affects infant attention in a free-play test and is related to change in blood pressure.	https://pubmed.ncbi.nlm.nih.gov/24045099
2014	24667866	Growth and fatty acid profiles of VLBW infants receiving a multicomponent lipid emulsion from birth.	https://pubmed.ncbi.nlm.nih.gov/24667866
2014	24345834	Dietary docosahexaenoic acid supplementation in children with autism.	https://pubmed.ncbi.nlm.nih.gov/24345834
2014	24427279	Omega-3 fatty acid deficiency in infants before birth identified using a randomized trial of maternal DHA supplementation in pregnancy.	https://pubmed.ncbi.nlm.nih.gov/24427279
2014	24508294	Clinical significance of neuropsychological improvement after supplementation with omega-3 in 8-12 years old malnourished Mexican children: a randomized, double-blind, placebo and treatment clinical trial.	https://pubmed.ncbi.nlm.nih.gov/24508294
2014	24522442	Randomized controlled trial of maternal omega-3 long-chain PUFA supplementation during pregnancy and early childhood development of attention, working memory, and inhibitory control.	https://pubmed.ncbi.nlm.nih.gov/24522442
2014	24689967	A randomized, controlled, crossover trial of fish oil treatment for impulsive aggression in children and adolescents with disruptive behavior disorders.	https://pubmed.ncbi.nlm.nih.gov/24689967
2015	25803546	Maternal fish oil supplementation in pregnancy: a 12 year follow-up of a randomised controlled trial.	https://pubmed.ncbi.nlm.nih.gov/25803546

2015	25988553	Effects of Maternal Ω-3 Supplementation on Fatty Acids and on Visual and Cognitive Development.	https://pubmed.ncbi.nlm.nih.gov/25988553
2015	26262896	Prenatal Docosahexaenoic Acid Supplementation and Offspring Development at 18 Months: Randomized Controlled Trial.	https://pubmed.ncbi.nlm.nih.gov/26262896
2015	25926416	Prenatal Supplementation with Docosahexaenoic Acid Has No Effect on Growth through 60 Months of Age.	https://pubmed.ncbi.nlm.nih.gov/25926416
2015	26646031	A randomized clinical trial of high eicosapentaenoic acid omega-3 fatty acids and inositol as monotherapy and in combination in the treatment of pediatric bipolar spectrum disorders: a pilot study.	https://pubmed.ncbi.nlm.nih.gov/26646031
2016	26561619	Folate and long-chain polyunsaturated fatty acid supplementation during pregnancy has long-term effects on the attention system of 8.5-y-old offspring: a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/26561619
2016	26573368	A randomised double-blind placebo-controlled trial investigating the behavioural effects of vitamin, mineral and n-3 fatty acid supplementation in typically developing adolescent schoolchildren.	https://pubmed.ncbi.nlm.nih.gov/26573368
2016	27053380	Reduction of the n-6:n-3 long-chain PUFA ratio during pregnancy and lactation on offspring body composition: follow-up results from a randomized controlled trial up to 5 y of age.	https://pubmed.ncbi.nlm.nih.gov/27053380

2016	27166583	Nutritional supplementation to reduce child aggression: a randomized, stratified, single-blind, factorial trial.	https://pubmed.ncbi.nlm.nih.gov/27166583
2016	27290652	The effect of prenatal docosahexaenoic acid supplementation on infant outcomes in African American women living in low-income environments: A randomized, controlled trial.	https://pubmed.ncbi.nlm.nih.gov/27290652
2016	27362506	Prenatal DHA supplementation and infant attention.	https://pubmed.ncbi.nlm.nih.gov/27362506
2016	27604770	Prenatal supplementation with DHA improves attention at 5 y of age: a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/27604770
2016	25747955	Omega-3 fatty acid supplementation affects pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebo-controlled trial.	https://pubmed.ncbi.nlm.nih.gov/25747955
2017	28437326	Favorable Outcomes of Preterm Infants With Parenteral Nutrition-associated Liver Disease Treated With Intravenous Fish Oil-based Lipid Emulsion.	https://pubmed.ncbi.nlm.nih.gov/28437326
2017	29072164	Effects of a lipid emulsion containing fish oil on polyunsaturated fatty acid profiles, growth and morbidities in extremely premature infants: A randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/29072164
2017	27747986	Event-related potential differences in children supplemented with long-chain polyunsaturated fatty acids during infancy.	https://pubmed.ncbi.nlm.nih.gov/27747986

2016	27914519	Growth and tolerance of infants fed formula with a new algal source of docosahexaenoic acid: Double-blind, randomized, controlled trial.	https://pubmed.ncbi.nlm.nih.gov/27914519
2016	28065179	Maternal fish oil supplementation during lactation is associated with reduced height at 13 years of age and higher blood pressure in boys only.	https://pubmed.ncbi.nlm.nih.gov/28065179
2017	28324081	Seven-Year Follow-up of Children Born to Women in a Randomized Trial of Prenatal DHA Supplementation.	https://pubmed.ncbi.nlm.nih.gov/28324081
2017	28549983	The effect of omega-3 supplementation on pregnancy outcomes by smoking status.	https://pubmed.ncbi.nlm.nih.gov/28549983
2017	28574453	Randomized Controlled Trial of DHA Supplementation during Pregnancy: Child Adiposity Outcomes.	https://pubmed.ncbi.nlm.nih.gov/28574453
2018	28752418	The effect of perinatal fish oil supplementation on neurodevelopment and growth of infants: a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/28752418
2017	28878181	Developmental Outcomes at 24 Months of Age in Toddlers Supplemented with Arachidonic Acid and Docosahexaenoic Acid: Results of a Double Blind Randomized, Controlled Trial.	https://pubmed.ncbi.nlm.nih.gov/28878181
2017	28969711	Fatty fish intake and attention performance in 14-15 year old adolescents: FINS-TEENS - a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/28969711
2017	27604240	Psychoeducational Psychotherapy and Omega-3 Supplementation Improve Co-Occurring Behavioral Problems in Youth	https://pubmed.ncbi.nlm.nih.gov/27604240

		with Depression: Results from a Pilot RCT.	
2018	29098783	Associations of maternal nutrition during pregnancy and post-partum with maternal cognition and caregiving.	https://pubmed.ncbi.nlm.nih.gov/29098783
2018	29462158	Docosahexaenoic acid for reading, working memory and behavior in UK children aged 7-9: A randomized controlled trial for replication (the DOLAB II study).	https://pubmed.ncbi.nlm.nih.gov/29462158
2018	29385062	A Randomized Double-Blinded, Placebo-Controlled Trial Investigating the Effect of Fish Oil Supplementation on Gene Expression Related to Insulin Action, Blood Lipids, and Inflammation in Gestational Diabetes Mellitus-Fish Oil Supplementation and Gestational Diabetes.	https://pubmed.ncbi.nlm.nih.gov/29385062
2018	29530020	Fatty fish intake and cognitive function: FINS-KIDS, a randomized controlled trial in preschool children.	https://pubmed.ncbi.nlm.nih.gov/29530020
2019	29617210	Effect of omega-3 fatty acids supplementation during pregnancy on lung function in preschoolers: a clinical trial.	https://pubmed.ncbi.nlm.nih.gov/29617210
2018	30181143	Effect of fish oil supplementation in pregnancy on bone, lean, and fat mass at six years: randomised clinical trial.	https://pubmed.ncbi.nlm.nih.gov/30181143
2018	29063592	Omega-3 supplementation associated with improved parent-rated executive function in youth with mood disorders: secondary analyses of the omega 3 and therapy (OATS) trials.	https://pubmed.ncbi.nlm.nih.gov/29063592

2019	30378203	Efficacy of a Mediterranean diet supplemented with fatty fish in ameliorating inflammation in paediatric asthma: a randomised controlled trial.	https://pubmed.ncbi.nlm.nih.gov/30378203
2019	30744880	A randomised controlled trial of vitamin D and omega-3 long chain polyunsaturated fatty acids in the treatment of irritability and hyperactivity among children with autism spectrum disorder.	https://pubmed.ncbi.nlm.nih.gov/30744880
2019	30418579	Fish Oil Supplementation in Pregnancy Increases Gestational Age, Size for Gestational Age, and Birth Weight in Infants: A Randomized Controlled Trial.	https://pubmed.ncbi.nlm.nih.gov/30418579
2019	30544211	Neither n-3 Long-Chain PUFA Supplementation of Mothers through Lactation nor of Offspring in a Complementary Food Affects Child Overall or Social-Emotional Development: A 2 × 2 Factorial Randomized Controlled Trial in Rural Ethiopia.	https://pubmed.ncbi.nlm.nih.gov/30544211
2019	30598384	The effect of Atlantic salmon consumption on the cognitive performance of preschool children - A randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/30598384
2019	31151199	Effect of 1 Year Krill Oil Supplementation on Cognitive Achievement of Dutch Adolescents: A Double-Blind Randomized Controlled Trial.	https://pubmed.ncbi.nlm.nih.gov/31151199
2019	31187863	Docosahexaenoic and Arachidonic Acid Supplementation of Toddlers Born Preterm Does Not Affect Short-Term Growth or Adiposity.	https://pubmed.ncbi.nlm.nih.gov/31187863

2019	31595295	Effects of oily fish intake on cardiometabolic markers in healthy 8- to 9-y-old children: the FiSK Junior randomized trial.	https://pubmed.ncbi.nlm.nih.gov/31595295
2020	32167792	Effects of Fish Oil Monotherapy on Depression and Prefrontal Neurochemistry in Adolescents at High Risk for Bipolar I Disorder: A 12-Week Placebo-Controlled Proton Magnetic Resonance Spectroscopy Trial.	https://pubmed.ncbi.nlm.nih.gov/32167792
2020	30380355	Impact of Omega-3 Fatty Acids Among Other Nonpharmacological Interventions on Behavior and Quality of Life in Children with Compromised Conduct in Spain.	https://pubmed.ncbi.nlm.nih.gov/30380355
2020	32590001	A Randomized Trial of Parenteral Nutrition Using a Mixed Lipid Emulsion Containing Fish Oil in Infants of Extremely Low Birth Weight: Neurodevelopmental Outcome at 12 and 24 Months Corrected Age, A Secondary Outcome Analysis.	https://pubmed.ncbi.nlm.nih.gov/32590001
2021	32222821	Omega-3 supplementation, child antisocial behavior, and psychopathic personality: a randomized, double-blind, placebo-controlled, stratified, parallel group trial.	https://pubmed.ncbi.nlm.nih.gov/32222821
2021	33599431	The effect of omega-3 fatty acids supplementation on social and behavioral disorders of children with autism: a randomized clinical trial.	https://pubmed.ncbi.nlm.nih.gov/33599431

2020	32312337	Do infants of breast-feeding mothers benefit from additional long-chain PUFA from fish oil? A 6-year follow-up.	https://pubmed.ncbi.nlm.nih.gov/32312337
2020	32529206	Effects of oily fish intake on cognitive and socioemotional function in healthy 8-9-year-old children: the FiSK Junior randomized trial.	https://pubmed.ncbi.nlm.nih.gov/32529206
2020	32899673	Effects of Maternal Fish Oil and/or 5-Methyl-Tetrahydrofolate Supplementation during Pregnancy on Offspring Brain Resting-State at 10 Years Old: A Follow-Up Study from the NUHEAL Randomized Controlled Trial.	https://pubmed.ncbi.nlm.nih.gov/32899673
2021	32979077	No effect of 6-month supplementation with 300 mg/d docosahexaenoic acid on executive functions among healthy school-aged children: a randomized, double-blind, placebo-controlled trial.	https://pubmed.ncbi.nlm.nih.gov/32979077
2020	33023067	Effect of Maternal Docosahexaenoic Acid (DHA) Supplementation on Offspring Neurodevelopment at 12 Months in India: A Randomized Controlled Trial.	https://pubmed.ncbi.nlm.nih.gov/33023067
2021	33506965	Fish Oil Supplementation in Pregnancy and Neurodevelopment in Childhood-A Randomized Clinical Trial.	https://pubmed.ncbi.nlm.nih.gov/33506965
2021	33572368	Effect of Omega-3 Supplementation in Pregnant Women with Obesity on Newborn Body Composition, Growth and Length of Gestation: A Randomized Controlled Pilot Study.	https://pubmed.ncbi.nlm.nih.gov/33572368

2021	33668849	Prenatal Maternal Docosahexaenoic Acid (DHA) Supplementation and Newborn Anthropometry in India: Findings from DHANI.	https://pubmed.ncbi.nlm.nih.gov/33668849
2021	34578873	The Influence of Prenatal DHA Supplementation on Individual Domains of Behavioral Functioning in School-Aged Children: Follow-Up of a Randomized Controlled Trial.	https://pubmed.ncbi.nlm.nih.gov/34578873
2022	35356726	Infant Formula Supplemented With Milk Fat Globule Membrane, Long-Chain Polyunsaturated Fatty Acids, and Synbiotics Is Associated With Neurocognitive Function and Brain Structure of Healthy Children Aged 6 Years: The COGNIS Study.	https://pubmed.ncbi.nlm.nih.gov/35356726
2022	35406010	Effect of Vitamin D and Docosahexaenoic Acid Co-Supplementation on Vitamin D Status, Body Composition, and Metabolic Markers in Obese Children: A Randomized, Double Blind, Controlled Study.	https://pubmed.ncbi.nlm.nih.gov/35406010
2022	34214231	Fish oil supplementation alters emotion-generated corticolimbic functional connectivity in depressed adolescents at high-risk for bipolar I disorder: A 12-week placebo-controlled fMRI trial.	https://pubmed.ncbi.nlm.nih.gov/34214231
2023	37202530	Lipid profile after omega-3 supplementation in neonates with intrauterine growth retardation: a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/37202530

Table 4: Studies meeting PICOTS, except for population

The following list includes studies with at least one outcome related to growth and/or development. Two scientists reviewed each study, and determined that all studies listed met the PICOTS criteria listed above, except for population. We believe it makes sense to exclude children with diagnosed ADHD for the purpose of studying cognitive outcomes. However, if the outcome being reviewed relates to growth, then these children may be classified as otherwise "normal" and "healthy," and the associated studies could be considered. **17 Studies Included.**

Year	PMID	Title	PubMed Link
2001	11487742	A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder.	https://pubmed.ncbi.nlm.nih.gov/11487742
2007	17629918	Effects of an open-label pilot study with high-dose EPA/DHA concentrates on plasma phospholipids and behavior in children with attention deficit hyperactivity disorder.	https://pubmed.ncbi.nlm.nih.gov/17629918
2009	18448859	Omega-3/omega-6 fatty acids for attention deficit hyperactivity disorder: a randomized placebo-controlled trial in children and adolescents.	https://pubmed.ncbi.nlm.nih.gov/18448859
2009	19436468	Omega-3 fatty acid treatment of children with attention-deficit hyperactivity disorder: A	https://pubmed.ncbi.nlm.nih.gov/19436468

		randomized, double-blind, placebo-controlled study.	
2010	20491709	EPA supplementation improves teacher-rated behaviour and oppositional symptoms in children with ADHD.	https://pubmed.ncbi.nlm.nih.gov/20491709
2012	22596014	Combined ω3 and ω6 supplementation in children with attention-deficit hyperactivity disorder (ADHD) refractory to methylphenidate treatment: a double-blind, placebo-controlled study.	https://pubmed.ncbi.nlm.nih.gov/22596014
2015	24214970	Increased Erythrocyte Eicosapentaenoic Acid and Docosahexaenoic Acid Are Associated With Improved Attention and Behavior in Children With ADHD in a Randomized Controlled Three-Way Crossover Trial.	https://pubmed.ncbi.nlm.nih.gov/24214970
2014	2495852	Effect of supplementation with long-chain ω-3 polyunsaturated fatty acids on behavior and cognition in children with attention deficit/hyperactivity disorder (ADHD): a randomized placebo-controlled intervention trial.	https://pubmed.ncbi.nlm.nih.gov/2495852

2015	25790022	Reduced Symptoms of Inattention after Dietary Omega-3 Fatty Acid Supplementation in Boys with and without Attention Deficit/Hyperactivity Disorder.	https://pubmed.ncbi.nlm.nih.gov/25790022
2014	25798168	Comparison of therapeutic effects of omega-3 and methylphenidate (ritalin(®)) in treating children with attention deficit hyperactivity disorder.	https://pubmed.ncbi.nlm.nih.gov/25798168
2015	26015389	Protective effects of dietary supplementation with natural ω-3 polyunsaturated fatty acids on the visual acuity of school-age children with lower IQ or attention-deficit hyperactivity disorder.	https://pubmed.ncbi.nlm.nih.gov/26015389
2015	26682998	Biochemical and Psychological Effects of Omega-3/6 Supplements in Male Adolescents with Attention-Deficit/Hyperactivity Disorder: A Randomized, Placebo-Controlled, Clinical Trial.	https://pubmed.ncbi.nlm.nih.gov/26682998

2017	27921139	Reduced inattention and hyperactivity and improved cognition after marine oil extract (PCSO-524®) supplementation in children and adolescents with clinical and subclinical symptoms of attention-deficit hyperactivity disorder (ADHD): a randomised, double-blind, placebo-controlled trial.	https://pubmed.ncbi.nlm.nih.gov/27921139
2018	28993963	A double-blind placebo-controlled randomised trial of omega-3 supplementation in children with moderate ADHD symptoms.	https://pubmed.ncbi.nlm.nih.gov/28993963
2019	30246216	Behavioral and cognitive effects of docosahexaenoic acid in drug-naïve children with attention-deficit/hyperactivity disorder: a randomized, placebo-controlled clinical trial.	https://pubmed.ncbi.nlm.nih.gov/30246216
2019	31745072	High-dose eicosapentaenoic acid (EPA) improves attention and vigilance in children and adolescents with attention deficit hyperactivity disorder (ADHD) and low endogenous EPA levels.	https://pubmed.ncbi.nlm.nih.gov/31745072

2021	32847461	Efficacy of Omega-3 and Korean Red Ginseng in Children with Subthreshold ADHD: A Double-Blind, Randomized, Placebo-Controlled Trial.	https://pubmed.ncbi.nlm.nih.gov/32847461
2022	34656505	Impulsiveness in children with attention-deficit/hyperactivity disorder after an 8-week intervention with the Mediterranean diet and/or omega-3 fatty acids: a randomised clinical trial.	https://pubmed.ncbi.nlm.nih.gov/34656505

Table 5: Studies meeting PICOTS, but not health conditions of the population
The following list includes studies with at least one outcome related to growth and/or development. Two scientists reviewed each study. While it may make sense to exclude some of these health conditions for the purpose of studying growth or development (i.e. cognitive outcomes), we believe that some of these studies may warrant further examination and review.
70 Studies Included.

Year	PMID	Title	PubMed Link
2007	18046087	Fish oil supplementation improves left ventricular function in children with idiopathic dilated cardiomyopathy.	https://pubmed.ncbi.nlm.nih.gov/18046087
2009	19214054	Omega-3 LC-PUFA supply and neurological outcomes in children with phenylketonuria (PKU).	https://pubmed.ncbi.nlm.nih.gov/19214054
2012	22237883	Short-term use of parenteral nutrition with a lipid emulsion containing a mixture of soybean oil, olive oil, medium-chain triglycerides, and fish oil: a randomized double-blind study in preterm infants.	https://pubmed.ncbi.nlm.nih.gov/22237883
2014	23546614	The consumption of n-3 polyunsaturated fatty acids differentially modulates gene expression of peroxisome proliferator-activated receptor alpha and gamma and hypoxia-inducible factor 1 alpha in subcutaneous adipose tissue of obese adolescents.	https://pubmed.ncbi.nlm.nih.gov/23546614
2014	23894176	Pediatric intestinal failure-associated liver disease is reversed with 6 months of intravenous fish oil.	https://pubmed.ncbi.nlm.nih.gov/23894176

2017	24464327	Efficacy and Safety of Omega-3/6 Fatty Acids, Methylphenidate, and a Combined Treatment in Children With ADHD.	https://pubmed.ncbi.nlm.nih.gov/24464327
2014	24505350	Role of docosahexaenoic acid treatment in improving liver histology in pediatric nonalcoholic fatty liver disease.	https://pubmed.ncbi.nlm.nih.gov/24505350
2012	24568073	Effect of n-3 supplementation on hyperactivity, oxidative stress and inflammatory mediators in children with attention-deficit-hyperactivity disorder.	https://pubmed.ncbi.nlm.nih.gov/24568073
2015	24973862	Effects of omega-3 fatty acid supplementation on insulin metabolism and lipid profiles in gestational diabetes: Randomized, double-blind, placebo-controlled trial.	https://pubmed.ncbi.nlm.nih.gov/24973862
2014	25240461	Altered erythrocyte membrane fatty acid profile in typical Rett syndrome: effects of omega-3 polyunsaturated fatty acid supplementation.	https://pubmed.ncbi.nlm.nih.gov/25240461
2016	26961929	Effect of ω-3 supplementation on placental lipid metabolism in overweight and obese women.	https://pubmed.ncbi.nlm.nih.gov/26961929
2017	27072591	Omega-3 LCPUFA supplement: a nutritional strategy to prevent maternal and neonatal oxidative stress.	https://pubmed.ncbi.nlm.nih.gov/27072591
2017	28748334	Effect of Omega-3 and -6 Supplementation on Language in Preterm Toddlers Exhibiting Autism Spectrum Disorder Symptoms.	https://pubmed.ncbi.nlm.nih.gov/28748334

2018	29460817	MaFOS-GDM trial: Maternal fish oil supplementation in women with gestational diabetes and cord blood DNA methylation at insulin like growth factor-1 (IGF-1) gene.	https://pubmed.ncbi.nlm.nih.gov/29460817
2018	29490101	ω-3 and ω-6 Fatty Acid Supplementation May Reduce Autism Symptoms Based on Parent Report in Preterm Toddlers.	https://pubmed.ncbi.nlm.nih.gov/29490101
2022	35644107	Effects of Omega-3-6-9 fatty acid supplementation on behavior and sleep in preterm toddlers with autism symptomatology: Secondary analysis of a randomized clinical trial.	https://pubmed.ncbi.nlm.nih.gov/35644107
2011	21362575	Parenteral nutrition of preterm infants with a lipid emulsion containing 10% fish oil: effect on plasma lipids and long-chain polyunsaturated fatty acids.	https://pubmed.ncbi.nlm.nih.gov/21362575
2001	11483801	Growth and development in preterm infants fed long-chain polyunsaturated fatty acids: a prospective, randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/11483801
2002	12412870	Dietary supplementation of long-chain polyunsaturated fatty acids in preterm infants: effects on cerebral maturation.	https://pubmed.ncbi.nlm.nih.gov/12412870
2003	12680858	Maternal fish oil supplementation in pregnancy reduces interleukin-13 levels in cord blood of infants at high risk of atopy.	https://pubmed.ncbi.nlm.nih.gov/12680858
2003	14639802	Influence of long-chain polyunsaturated fatty acid formula feeds on vitamin E status in preterm infants.	https://pubmed.ncbi.nlm.nih.gov/14639802

2006	16750345	Docosahexaenoic acid administered in the acute phase protects the nutritional status of septic neonates.	https://pubmed.ncbi.nlm.nih.gov/16750345
2007	17452220	Effect of fish oil supplementation on fatty acid status, coordination, and fine motor skills in children with phenylketonuria.	https://pubmed.ncbi.nlm.nih.gov/17452220
2008	18519483	Improved cognitive development among preterm infants attributable to early supplementation of human milk with docosahexaenoic acid and arachidonic acid.	https://pubmed.ncbi.nlm.nih.gov/18519483
2008	18842793	Higher dose of docosahexaenoic acid in the neonatal period improves visual acuity of preterm infants: results of a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/18842793
2009	19489765	Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy.	https://pubmed.ncbi.nlm.nih.gov/19489765
2009	19515739	Dietary supplementation with n-3 polyunsaturated fatty acids in early childhood: effects on blood pressure and arterial structure and function at age 8 y.	https://pubmed.ncbi.nlm.nih.gov/19515739
2009	19615874	Does dietary DHA improve neural function in children? Observations in phenylketonuria.	https://pubmed.ncbi.nlm.nih.gov/19615874
2010	20227721	The impact of early nutrition on incidence of allergic manifestations and common respiratory illnesses in children.	https://pubmed.ncbi.nlm.nih.gov/20227721

2011	20359723	Circulating visfatin levels in healthy preterm infants are independently associated with high-density lipoprotein cholesterol levels and dietary long-chain polyunsaturated fatty acids.	https://pubmed.ncbi.nlm.nih.gov/20359723
2010	20545703	Impact of a novel nutritional formula on asthma control and biomarkers of allergic airway inflammation in children.	https://pubmed.ncbi.nlm.nih.gov/20545703
2011	21807696	Prenatal docosahexaenoic acid supplementation and infant morbidity: randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/21807696
2011	21941411	DHA supplementation during pregnancy and lactation affects infants' cellular but not humoral immune response.	https://pubmed.ncbi.nlm.nih.gov/21941411
2012	22047909	Enhanced prostaglandin F2α formation in human pregnancy and the effect of increased oily fish intake: results from the Salmon in Pregnancy Study.	https://pubmed.ncbi.nlm.nih.gov/22047909
2012	22552037	Fish-oil supplementation in pregnancy does not reduce the risk of gestational diabetes or preeclampsia.	https://pubmed.ncbi.nlm.nih.gov/22552037
2013	23761484	Modulation of DNA methylation states and infant immune system by dietary supplementation with ω-3 PUFA during pregnancy in an intervention study.	https://pubmed.ncbi.nlm.nih.gov/23761484
2014	24614142	Effects of growing-up milk supplemented with prebiotics and LCPUFAs on infections in young children.	https://pubmed.ncbi.nlm.nih.gov/24614142

2014	25293351	Dietary supplementation with polyunsaturated fatty acid during pregnancy modulates DNA methylation at IGF2/H19 imprinted genes and growth of infants.	https://pubmed.ncbi.nlm.nih.gov/25293351
2015	26026214	A double-blind, placebo-controlled randomized trial to evaluate the efficacy of docosahexaenoic acid supplementation on hepatic fat and associated cardiovascular risk factors in overweight children with nonalcoholic fatty liver disease.	https://pubmed.ncbi.nlm.nih.gov/26026214
2016	26846324	Daily Enteral DHA Supplementation Alleviates Deficiency in Premature Infants.	https://pubmed.ncbi.nlm.nih.gov/26846324
2016	26939082	Diffusion tensor imaging and behavior in premature infants at 8 years of age, a randomized controlled trial with long-chain polyunsaturated fatty acids.	https://pubmed.ncbi.nlm.nih.gov/26939082
2016	27155920	The role of free fatty acids in the inflammatory and cardiometabolic profile in adolescents with metabolic syndrome engaged in interdisciplinary therapy.	https://pubmed.ncbi.nlm.nih.gov/27155920
2016	27822319	Effect of prenatal DHA supplementation on the infant epigenome: results from a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/27822319
2017	27893018	Effect of ω-3 Polyunsaturated Fatty Acids in Young People at Ultrahigh Risk for Psychotic Disorders: The NEURAPRO Randomized Clinical Trial.	https://pubmed.ncbi.nlm.nih.gov/27893018
2017	28355511	Docosahexaenoic Acid and Bronchopulmonary Dysplasia in Preterm Infants.	https://pubmed.ncbi.nlm.nih.gov/28355511

2017	28378851	Effect of eicosapentaenoic acid and docosahexaenoic acid supplementation on C-peptide preservation in pregnant women with type-1 diabetes: randomized placebo controlled clinical trial.	https://pubmed.ncbi.nlm.nih.gov/28378851
2017	28727654	Growth and Nutritional Biomarkers of Preterm Infants Fed a New Powdered Human Milk Fortifier: A Randomized Trial.	https://pubmed.ncbi.nlm.nih.gov/28727654
2018	29023666	Nutritional intervention and neurodevelopmental outcome in infants with suspected cerebral palsy: the Dolphin infant double-blind randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/29023666
2018	29681953	Omega-3 Fatty Acid Supplementation Improves Heart Rate Variability in Obese Children.	https://pubmed.ncbi.nlm.nih.gov/29681953
2018	29884682	Cardiometabolic Risk Factors at 5 Years After Omega-3 Fatty Acid Supplementation in Infancy.	https://pubmed.ncbi.nlm.nih.gov/29884682
2018	30392581	Randomized controlled trial of brain specific fatty acid supplementation in pregnant women increases brain volumes on MRI scans of their newborn infants.	https://pubmed.ncbi.nlm.nih.gov/30392581
2019	30411372	Long-Term Outcomes in Children With Intestinal Failure-Associated Liver Disease Treated With 6 Months of Intravenous Fish Oil Followed by Resumption of Intravenous Soybean Oil.	https://pubmed.ncbi.nlm.nih.gov/30411372
2019	30765737	Nutritional and lipidomics biomarkers of docosahexaenoic acid-based multivitamin therapy in pediatric NASH.	https://pubmed.ncbi.nlm.nih.gov/30765737

2019	31070712	Docosahexaenoic acid supplementation of preterm infants and parent-reported symptoms of allergic disease at 7 years corrected age: follow-up of a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/31070712
2019	31509674	A Randomized Trial of Prenatal n-3 Fatty Acid Supplementation and Preterm Delivery.	https://pubmed.ncbi.nlm.nih.gov/31509674
2020	31978030	Growth in Infants and Children With Intestinal Failure-associated Liver Disease Treated With Intravenous Fish Oil.	https://pubmed.ncbi.nlm.nih.gov/31978030
2020	32453393	Supplementation with vitamin D or ω-3 fatty acids in adolescent girls and young women with endometriosis (SAGE): a double-blind, randomized, placebo-controlled trial.	https://pubmed.ncbi.nlm.nih.gov/32453393
2020	33019398	Effect of Omega-3 supplements on quality of life among children on dialysis: A prospective cohort study.	https://pubmed.ncbi.nlm.nih.gov/33019398
2021	33152314	The effects of a combined intervention (docosahexaenoic acid supplementation and home-based dietary counseling) on metabolic control in obese and overweight pregnant women: the MIGHT study.	https://pubmed.ncbi.nlm.nih.gov/33152314
2020	33339438	Multiple Micronutrients, Lutein, and Docosahexaenoic Acid Supplementation during Lactation: A Randomized Controlled Trial.	https://pubmed.ncbi.nlm.nih.gov/33339438
2020	33680026	Effects of Fish Oil Supplementation on Pregnancy Outcomes in Pregnant Women Referred to Kosar Hospital.	https://pubmed.ncbi.nlm.nih.gov/33680026

2021	34459776	CONDITION OF FETURES AND NEWBORNS FROM WOMEN WITH INFERTILITY TREATED WITH ASSISTED REPRODUCTIVE TECHNOLOGIES AND WITH CONCOMITANT INTRAHEPATIC CHOLESTASIS.	https://pubmed.ncbi.nlm.nih.gov/34459776
2011	20624152	Attention among very low birth weight infants following early supplementation with docosahexaenoic and arachidonic acid.	https://pubmed.ncbi.nlm.nih.gov/20624152
2013	23266209	A randomized placebo-controlled study on high-dose oral algal docosahexaenoic acid supplementation in children with cystic fibrosis.	https://pubmed.ncbi.nlm.nih.gov/23266209
2015	25986018	Long-chain polyunsaturated fatty acids and cognition in VLBW infants at 8 years: an RCT.	https://pubmed.ncbi.nlm.nih.gov/25986018
2016	26537943	Long-term effect of high-dose supplementation with DHA on visual function at school age in children born at <33 wk gestational age: results from a follow-up of a randomized controlled trial.	https://pubmed.ncbi.nlm.nih.gov/26537943
2016	27658130	One month of omega-3 fatty acid supplementation improves lipid profiles, glucose levels and blood pressure in overweight schoolchildren with metabolic syndrome.	https://pubmed.ncbi.nlm.nih.gov/27658130
2018	29269199	A Mixed Lipid Emulsion for Prevention of Parenteral Nutrition Associated Cholestasis in Extremely Low Birth Weight Infants: A Randomized Clinical Trial.	https://pubmed.ncbi.nlm.nih.gov/29269199

2019	31030946	A Mixed Lipid Emulsion Containing Fish Oil and Its Effect on Electrophysiological Brain Maturation in Infants of Extremely Low Birth Weight: A Secondary Analysis of a Randomized Clinical Trial.	https://pubmed.ncbi.nlm.nih.gov/31030946
2021	34210228	Supplementation of EPA and DHA in pregnant women with type 1 diabetes mellitus.	https://pubmed.ncbi.nlm.nih.gov/34210228

Table 6: Studies meeting PICOTS, but not population, as per the study title
The following list includes studies with at least one outcome related to growth and/or development. Two scientists reviewed each study, and, based on the title, it was not clear if the study population met AHRQ's criteria. Then, the Abstracts were reviewed, and the following list of studies was compiled. These studies warrant further evaluation to determine if they should be considered. **12 Studies Included.**

Year	PMID	Title	PubMed Link
2007	18158838	A 5-month open study with long-chain polyunsaturated fatty acids in dyslexia.	https://pubmed.ncbi.nlm.nih.gov/18158838
2004	14985685	Effect of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder - a placebo-controlled double-blind study.	https://pubmed.ncbi.nlm.nih.gov/14985685
2015	26339616	Effect of Docosahexaenoic Acid on Apoptosis and Proliferation in the Placenta: Preliminary Report.	https://pubmed.ncbi.nlm.nih.gov/26339616
2019	30614004	Enteral Docosahexaenoic Acid and Retinopathy of Prematurity: A Randomized Clinical Trial.	https://pubmed.ncbi.nlm.nih.gov/30614004/
2021	33523106	Effect of Enteral Lipid Supplement on Severe Retinopathy of	https://pubmed.ncbi.nlm.nih.gov/33523106

		Prematurity: A Randomized Clinical Trial.	
2020	30345864	Addition of sildenafil citrate for treatment of severe intrauterine growth restriction: a double blind randomized placebo controlled trial.	https://pubmed.ncbi.nlm.nih.gov/30345864
2015	25804268	Omega-3 fatty acids in the management of autism spectrum disorders: findings from an open-label pilot study in Singapore.	https://pubmed.ncbi.nlm.nih.gov/25804268
2010	20124114	Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial.	https://pubmed.ncbi.nlm.nih.gov/20124114
2020	32121236	Inflammation (IL-1β) Modifies the Effect of Vitamin D and Omega-3 Long Chain Polyunsaturated Fatty Acids on Core Symptoms of Autism Spectrum Disorder-An Exploratory Pilot Study.	https://pubmed.ncbi.nlm.nih.gov/32121236

2016	26077874	Effects of Iron Supplementation With and Without Docosahexaenoic Acid on the Cardiovascular Disease Risk Based on Paraoxonase-1, hs-CRP, and ApoB/ApoA-I Ratio in Women with Iron Deficiency Anemia.	https://pubmed.ncbi.nlm.nih.gov/26077874
2020	32887793	Fatty Acid Supplementation and Socioemotional Outcomes: Secondary Analysis of a Randomized Trial.	https://pubmed.ncbi.nlm.nih.gov/32887793
2012	22585765	A double-blind, placebo-controlled trial of ω-3 fatty acids in Tourette's disorder.	https://pubmed.ncbi.nlm.nih.gov/22585765

In addition to the study lists we have provided, we thought it was important to point to another study. A systematic review on the association between omega-3 consumption and cognitive outcomes was published recently and the studies listed in its reference list are relevant to Q2 and Q4.

Sherzai D, Moness R, Sherzai S, Sherzai A. A Systematic Review of Omega-3 Fatty Acid Consumption and Cognitive Outcomes in Neurodevelopment. Am J Lifestyle Med. 2022 Nov 16;17(5):649-685. doi: 10.1177/15598276221116052. PMID: 37711355; PMCID: PMC10498982.
https://pmc.ncbi.nlm.nih.gov/articles/PMC10498982/

GLOBAL ORGANIZATION FOR EPA AND DHA OMEGA-3S

GOED appreciates the opportunity to provide feedback on this protocol. We remain at your disposal should any questions arise.

Sincerely,

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