The Journal of Nutrition
Nutritional Epidemiology

n–3 Fatty Acid Supplementation in Mothers, Preterm Infants, and Term Infants and Childhood Psychomotor and Visual Development: A Systematic Review and Meta-Analysis

Masha Shulkin,[1,2] Laura Pimpin,[1] David Bellinger,[3,4,5] Sarah Kranz,[1] Wafaie Fawzi,[5] Christopher Duggan,[3,5] and Dariush Mozaffarian[1]

[1]Tufts Friedman School of Nutrition & Science Policy, Boston, MA; [2]University of Michigan Medical School, Ann Arbor, MI; [3]Boston Children's Hospital, Boston, MA; [4]Harvard Medical School, Boston, MA; and [5]Harvard TH Chan School of Public Health, Boston, MA

Abstract

Background: Epidemiologic studies link maternal seafood and n–3 (ω-3) polyunsaturated fatty acid (PUFA) consumption with improved childhood cognitive development; trials show mixed results.

Objective: We investigated effects of n–3 PUFA supplementation on child cognitive and visual outcomes.

Methods: We systematically reviewed and meta-analyzed randomized controlled trials of n–3 PUFA supplementation in mothers or infants (age $\leq$2 y) and evaluated standardized measures of cognitive or visual development up to age 18 y. Of 6286 abstracts and 669 full-text articles, 38 trials with 53 intervention arms were included. Data were extracted independently in duplicate. Findings were pooled using random-effects meta-analysis across supplementation periods (maternal, preterm, term infant); we also explored subgroup analyses stratified by supplementation period. Heterogeneity was explored using I^2, stratified analysis, and meta-regression. Cognitive development was assessed by Bayley Scales of Infant Development mental and psychomotor developmental indexes (MDI, PDI) and intelligence quotient (IQ); visual acuity was assessed by electrophysiological or behavioral measures.

Results: The 38 trials (mothers: $n = 13$; preterm infants: $n = 7$; term infants: $n = 18$) included 5541 participants. When we explored effects during different periods of supplementation, n–3 PUFA supplementation improved MDI in preterm infants (3.33; 95% CI: 0.72, 5.93), without statistically significant effects on PDI or IQ in different intervention period subgroups. Visual acuity [measured as the logarithm of the minimum angle of resolution (logMAR)] was improved by supplementation in preterm (–0.08 logMAR; 95% CI: –0.14, –0.01 logMAR) and term infants (–0.08 logMAR; 95% CI: –0.11, –0.05 logMAR), with a nonsignificant trend for maternal supplementation (–0.02 logMAR; 95% CI: –0.04, 0.00 logMAR). In main analyses pooling all supplementation periods, compared with placebo, n–3 PUFA supplementation improved MDI ($n = 21$ trials; 0.91; 95% CI: 0.005, 1.81; $P = 0.049$), PDI ($n = 21$ trials; 1.06 higher index; 95% CI: 0.10, 2.03; $P = 0.031$), and visual acuity ($n = 24$; –0.063 logMAR; 95% CI: –0.084, –0.041 logMAR; $P < 0.001$) but not IQ ($n = 7$; 0.20; 95% CI: –1.56, 1.96, $P = 0.83$), although few studies assessed this endpoint. Potential publication bias was identified for MDI (Eggers $P = 0.005$), but not other endpoints. Significant differences in findings were not identified by world region, race, maternal education, age at outcome assessment, supplementation duration, DHA or EPA dose, DHA:AA ratio, or study quality score (P-interaction > 0.05 each).

Conclusions: n–3 PUFA supplementation improves childhood psychomotor and visual development, without significant effects on global IQ later in childhood, although the latter conclusion is based on fewer studies. *J Nutr* 2018;148:409–418.

Keywords: long-chain n–3 polyunsaturated fatty acids, supplementation trials, prenatal, infant formula, cognition, development, Bayley Scales of Infant Development, visual acuity, childhood, meta-analysis

Manuscript received May 8, 2017. Initial review completed June 5, 2017. Revision accepted October 31, 2017.
First published online March 12, 2018; doi: https://doi.org/10.1093/jn/nxx031.

Introduction

DHA, a long-chain n–3 PUFA, is actively incorporated into brain and retinal cell membranes during the last trimester of pregnancy and the first 2 y of life, where it appears to play both structural and functional roles (1–4). While DHA can be synthesized in small amounts by humans from its essential fatty acid precursor, α-linolenic acid, the efficiency of this conversion is very low (5). Thus, adequate dietary DHA may be essential for optimal cognitive and visual development (6). Understanding the presence and magnitude of such potential benefit is crucial given low n–3 PUFA consumption worldwide: mean intakes in ~80% of women are <250 mg/d (7).

In prospective observational studies, the children of mothers with higher prenatal consumption of seafood and dietary n–3 PUFAs exhibit better cognitive outcomes (8, 9). In the first 2 y of life, dietary DHA appears to be of continued relevance due to ongoing significant brain development (10, 11). Dietary DHA may be particularly important for preterm infants, who experience fewer crucial late-pregnancy weeks of DHA accumulation in utero. Based on these observations, several trials of maternal or infant n–3 PUFA supplementation have been performed, including meta-analyses of these trials (12–19). Results have been mixed, precluding strong conclusions. Discrepant findings could partly relate to insufficient size and statistical power of some studies; variation in the period of supplementation (maternal, preterm infants, term infants); differences in other intervention characteristics (e.g., duration, dose); or failure to include more recently published trials. Prior meta-analyses have not consistently assessed these or other factors which might influence heterogeneity. Thus, the true benefits of maternal or infant n–3 PUFA supplementation for cognitive and visual development, and the factors that might influence such effects, remain unclear.

To address these critical questions, we performed a systematic review and meta-analysis to investigate the effects of maternal, preterm infant, and term infant n–3 PUFA supplementation on childhood cognitive and visual development.

Methods

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines during all stages of design, implementation, and reporting of this meta-analysis (20).

Primary exposure and outcomes. The primary exposure of interest was supplementation with n–3 PUFAs, including DHA or EPA (as well as both), via supplements, fortified foods, or diet in pregnant or lactating women or in infants aged <2 y. Our primary outcomes of interest were standardized measures of cognition and visual development in infants and children, followed up to age 18 y.

Search strategy. We performed electronic searches of PubMed (www.ncbi.nlm.nih.go/pubmed), PsycINFO (http://search.proquest.com/psycinfo), EMBASE (www.ovid.com/embase), the Cochrane Library (www.thecochranelibrary.com), and clinicaltrials.gov (www.clinicaltrials.gov), without language restrictions, from the earliest indexing year through 14 April 2016; see **Supplemental Methods 1** for details. Examples of search terms included *omega-3 fatty acids*, *polyunsaturated fatty acids*, *docosahexaenoic acid*, *eicosapentaenoic acid*, *fish*, *seafood*, *neurodevelopment*, *cognition*, *development*, *vision*, *child*, *infant*, *pregnancy*, and *lactation*. Following these electronic searches, for all final included publications and identified review articles, we hand-searched the citation lists as well as the first 20 "related references" on PubMed for additional eligible papers.

Study selection, inclusion, and exclusion criteria. Titles and abstracts of all identified articles were screened by one investigator (MS). For all potentially relevant articles, the full text was retrieved and reviewed independently and in duplicate by 2 investigators (MS, SK) according to specified eligibility criteria. Discrepancies were resolved by consensus or by a third investigator (LP). When duplicate publications were identified, the report including the latest follow-up for each outcome (domain) of interest was selected.

Studies were eligible for inclusion if they met the following criteria: *1*) were randomized controlled trials of supplementation or fortification with n–3 PUFA (DHA, EPA or a combination, with or without other n–3 or n–6 PUFAs) for ≥3 mo in pregnant mothers, nursing mothers, or children aged <2 y; *2*) evaluated generally healthy subjects in whom supplementation was not used as a treatment or secondary prevention; and *3*) assessed cognitive or visual development using a quantitative and standardized measure and reported findings to determine differences in group mean values at follow-up. Relevant infant development measures included the Bayley Scales of Infant Development (BSID); intelligence quotient (IQ) based on the Wechsler Intelligence Scale for Children, the Wechsler Preschool and Primary Scale of Intelligence, the Wechsler Abbreviated Scale of Intelligence, the Kaufman Assessment Battery for Children, and Stanford-Binet; and visual acuity based on electrophysiological measures such as visual evoked potentials (VEPs) and behavioral measures such as Teller Acuity Cards and acuity testing using HOTV optotypes.

We excluded observational studies, cross-sectional ecological studies, commentaries, general reviews, or case reports. We excluded trials evaluating n–3 PUFA treatment in clinical populations with chronic conditions, such as in diagnosed attention deficit hyperactivity disorder, autism spectrum disorder, or HIV (we included one trial in infants diagnosed with phenylketonuria at birth, who were otherwise healthy); trials that compared breastfed to formula-fed infants, given other potential differences between these interventions; trials in which an additional nutrition intervention was imbalanced between groups; and trials without a quantitative measure of n–3 PUFA dosing.

Data extraction and quality assessment. Data were extracted independently and in duplicate by 2 investigators (MS, SK) using a standardized and piloted electronic spreadsheet (Google); any differences were resolved by consensus. Information was extracted on the study (first author, corresponding author, contact information, publication year), setting (trial name, location, year), population (sample size, baseline age, gender, race/ethnicity, socioeconomic status, education, proportion breast or formula fed), intervention (duration, frequency, source of n–3 PUFA, method of supplementation, doses of DHA, EPA, arachidonic acid (AA), α-linolenic acid, and linoleic acid, compound given to both intervention and control, type of control, compliance, drop-out), outcomes (type of test, age at assessment, mean values, and statistical uncertainty), and quality score using the Cochrane Risk of Bias tool (21). For the latter, each of 6 criteria (excluding the "other bias" criterion; see **Supplemental Table 1**) was scored as low (+1), high (–1), or unclear (0) risk of bias; these values were summed to generate an

Supported by the Bill & Melinda Gates Foundation (grant OPP1099505). CD was supported in part by the NIH K24 DK104676. The funders had no role in the design and conduct of this study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of this manuscript.
Author disclosures: DM, ad hoc honoraria or consulting from Boston Heart Diagnostics, Haas Avocado Board, Astra Zeneca, Acasti Pharma, GOED, DSM, and Life Sciences Research Organization, and chapter royalties from UpToDate; MS, LP, DB, SK, WF, and CD, no conflicts of interest.
Supplemental Methods 1 and 2, Supplemental Tables 1–5, and Supplemental Figures 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/. Preliminary results presented in abstract form at Experimental Biology, April 2016 in San Diego, CA.
Address correspondence to DM (email: dariush.mozaffarian@tufts.edu).
Abbreviations used: BSID, Bayley Scales of Infant Development; IQ, intelligence quotient; logMAR, logarithm of the minimum angle of resolution; MDI, mental developmental index; PDI, psychomotor developmental index; VEP, visual evoked potential.

overall quality score. When a trial reported the same type of test at multiple time points [e.g., Bayley mental developmental index (MDI) at both 12 mo and at 24 mo in the same sample], we used the results at the latest age of follow-up.

Missing information was obtained by direct author contact (Supplemental Methods 1) or, if necessary, estimated from figures using Plot Digitizer (http://plotdigitizer.sourceforge.net/). Median and corresponding measures of uncertainty (e.g., SE, IQR, or 95% CI) were extracted when the primary metrics (i.e., mean and SD) were not reported. These suboptimal metrics were converted to mean and SD using a standardized approach described in **Supplemental Methods 2**. Visual acuity results reported in cycles/degree were extracted and converted to the logarithm of the minimum angle of resolution (logMAR) as described in Supplemental Methods 2. Use of BSID-III results is described in Supplemental Methods 2.

Data synthesis and statistical analysis. Following our prespecified analysis plan, findings were evaluated and pooled across supplementation periods (maternal, preterm, term infant); we also explored analyses stratified by supplementation period. Supplement doses were standardized to mg/d (maternal supplementation) or % of total fatty acids (%FA) (infant supplementation). Outcomes were pooled by domain, including MDI, psychomotor developmental index (PDI), overall IQ, and visual acuity in logMAR (15) (Supplemental Methods 2). Outcomes were evaluated as mean differences at follow-up (i.e., difference in follow-up mean test scores between intervention and control) with corresponding 95% CIs. Findings were pooled using inverse-variance weighted, random-effects meta-analysis (22). Heterogeneity between studies was quantified using the I^2 statistic. In addition to intervention period (maternal, preterm, term), prespecified subgroup analyses explored potential heterogeneity by world region, race, maternal education, age of outcome assessment, supplementation duration, DHA or EPA dose, DHA: AA ratio, type of placebo, and study quality score. Potential publication bias was assessed by visual inspection of funnel plots and Egger's test (23). If publication bias was identified, we used Duval and Tweedie's nonparametric trim-and-fill method to estimate the number and impact of hypothetically missing studies and derive an adjusted pooled estimate (24). Analyses were conducted using Stata 13.1 (StataCorp), 2-tailed $\alpha = 0.05$.

Results

Study characteristics. From 6286 unique abstracts and 669 full-text articles, we identified 44 publications reporting on 38 trials and including a total of 53 intervention arms (**Supplemental Figure 1**). These trials included 5541 unique participants, with 13 trials on mothers, 7 on preterm infants, and 18 on term infants (**Table 1**, **Supplemental Tables 2–4**) (25–72). Most trials were performed in high-income countries,

TABLE 1 Summary of characteristics of 38 randomized controlled trials including 53 intervention arms testing effects of long-chain n–3 PUFA supplementation on childhood cognitive and visual development[1]

Characteristics	Maternal ($n = 13$)	Preterm infant ($n = 7$)	Term infant ($n = 18$)
Location	Australia ($n = 3$), Bangladesh ($n = 1$), Mexico ($n = 1$), USA/Canada ($n = 3$), Western Europe ($n = 5$)[2]	Australia ($n = 1$), Mixed ($n = 2$),[3] Taiwan ($n = 1$), USA ($n = 1$), Western Europe ($n = 2$)	Australia ($n = 3$), China ($n = 1$), USA ($n = 10$), Western Europe ($n = 4$)
Total participants,[4] *n*	2852	942	1747
Participants per trial, *n*	190 (26–730)	105 (23–346)	91.9 (26–287)
Baseline age[5]	29.4 (22.7–33.2) y	30.7 (29–35.6)[6] wk gestation at birth	From birth ($n = 13$),[7] after ≤ 6 wk of breastfeeding ($n = 3$),[8] after 4–6 mo of breastfeeding ($n = 2$)
Race/ethnicity[9]	Asian ($n = 1$), black ($n = 1$), Hispanic ($n = 1$), white ($n = 10$)	Asian ($n = 1$), black ($n = 1$), white ($n = 4$), missing ($n = 1$)	Asian ($n = 1$), black ($n = 2$), white ($n = 14$), missing ($n = 1$)
Maternal education level[10]	High ($n = 5$), average ($n = 6$), low ($n = 1$), missing ($n = 1$)	Low ($n = 1$), missing ($n = 6$)	High ($n = 6$), average ($n = 2$), low ($n = 3$), missing ($n = 7$)
Supplementation period	Pregnancy only ($n = 7$), pregnancy plus 3–4 mo lactation ($n = 3$), lactation only ($n = 3$)	By 32 wk gestation ($n = 2$), within 1 mo of birth ($n = 4$), within 2 mo of birth ($n = 1$)[11]	Within 1 wk of birth ($n = 13$),[12] within days of PKU diagnosis ($n = 1$), after weaning ($n = 4$)
Supplementation duration, wk	21.8 (12.0–36.4)	45.3 (27–61.9)	37.2 (13.6–52.0)
DHA, mg/d	673 (200–2200)		
EPA,[13] mg/d	279 (0–1800)		
AA,[13] mg/d	—[14]		
DHA, %FA		0.28 (0.05–0.5)	0.38 (0.1–0.96)[15]
EPA,[14] %FA		0.12 (0–0.65)	0.05 (0–0.58)[15]
AA,[14] %FA		0.34 (0–0.7)	0.40 (0–0.72)[15]
Type of control	Vegetable oil ($n = 10$), fortified food without DHA/EPA ($n = 3$)	Formula ($n = 7$)	Formula ($n = 10$), olive oil ($n = 1$), fortified food without DHA/EPA ($n = 1$)
Outcomes assessed[16]	BSID ($n = 6$), K-ABC[17] ($n = 2$), TAC[18] ($n = 2$), VEP[19] ($n = 4$), WISC ($n = 1$)	BSID ($n = 5$), TAC ($n = 2$), VEP ($n = 3$), WASI ($n = 1$),	BSID ($n = 10$), HOTV[19] ($n = 1$), Stanford-Binet ($n = 1$), TAC ($n = 3$), VEP ($n = 8$), WPPSI ($n = 2$)
Latest age at outcome assessment,[20] median (min-max) months % dropout	BSID: 18 (10–30)IQ: 84 (81–144) Visual acuity: 4 (2–64) 33.3 (1.5–58)	BSID: 18 (12–24)IQ: 130 ($n = 1$) Visual acuity: 6 (4–24) 34.8 (11.5–74.5)	BSID: 18 (6–24)IQ: 48 (39–70) Visual acuity: 12 (4–48) 32.8 (7–65)

(*Continued*)

TABLE 1 *Continued*

Characteristics	Maternal ($n = 13$)	Preterm infant ($n = 7$)	Term infant ($n = 18$)
Quality score,[20] mean (min, max) out of a range of –6 to 6	3.6 (2–6)	3.1 (0–6)	2.6 (0–4)

[1] Values are the number of trials (*N*) or the mean value among trials (min, max) unless otherwise noted. Trial-specific characteristics (e.g., participant demographics) are reported by trial ($n = 38$). Intervention arm characteristics (e.g., dose) are reported by intervention arm ($n = 53$, including 17 maternal, 9 preterm, and 17 term infants). Outcome characteristics (e.g., outcomes assessed, age, sample size) are reported by end point. We also identified 3 trials in 2 publications (62, 64) that supplemented school-aged children (age >2 y); these are not included here. See Supplemental Tables 2–4 for study characteristics by individual publication. AA, arachidonic acid; BSID, Bayley Scales of Infant Development; HOTV, distance visual acuity testing using HOTV optotype chart; IQ, intelligence quotient; K-ABC, Kaufman Assessment Battery for Children; logMAR, logarithm of the minimum angle of resolution; max, maximum; MDI, mental developmental index; min, minimum; MPC, mental processing composite; PDI, psychomotor developmental index; PKU, phenylketonuria; TAC, Teller Acuity Card; VEP, visual evoked potential; WASI, Wechsler Abbreviated Scale of Intelligence; WISC, Wechsler Intelligence Scale for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; %FA, percentage fatty acids.

[2] Including one trial performed in 3 European study centers in Germany, Spain, and Hungary.

[3] USA, Chile, and UK ($n = 1$); USA and Chile ($n = 1$).

[4] No. of participants with the outcome of interest. Only participants at the latest age of evaluation for each outcome were included in each trial, to avoid double counting when multiple outcomes or multiple publications were reported per trial. If multiple outcomes were reported at the same age, the smallest sample size was included in this sum. Dropout was high in some trials (e.g., up to 72% in some intervention arms); thus, the total number of participants enrolled in these 38 trials was substantially greater than reported here.

[5] Minimum and maximum of study means.

[6] Excluding the one trial (42) performed in older preterm infants (born at 35.6 wk gestation, on average), the mean (min-max) baseline age was 29.9 (29–30.8) wk gestation at birth.

[7] As long as supplementation began within 10 d of birth, we considered baseline as 0 wk when calculating supplementation duration for each trial.

[8] In one trial in infants diagnosed with PKU (26), weaning was discouraged until 20 wk, and ~30% of infants received some breast milk after diagnosis [mean (min-max): 19 (8–39) d old].

[9] Represents the predominant racial/ethnic group. In 21 trials (9 maternal, 8 term infant, 4 preterm infant) that did not report racial composition, we assumed the predominant racial group in that country if the country was racially relatively homogeneous. US trials not reporting racial composition (47, 69) were not reclassified for this table.

[10] Education was categorized as follows: *1*) low: not completing high school, mean <12 y of education, score of 0–2 on 7-point education classification scale; *2*) average: high school diploma or some college/technical degree, mean 12–13.9 y of education, score of 3–4; *3*) high: completing college or higher degree, mean ≥14 y of education, score of 4–6, ≥60% completed college. Some studies reported education as a percentage of the sample completing a given level (e.g., 45% completed high school) without information about the composition of the remainder of the sample; in such cases, we classified trials using our best judgment, tending towards a conservative classification (average education) when classification was not obvious.

[11] Most participants began supplementation within 1 mo of birth; mean (min-max): 14 (1–60) d old.

[12] Because one trial (37) did not specify supplementation start date, we assumed trial feeding began at birth because the study recruited only mothers intending to formula-feed.

[13] All trials contained DHA, and some trials additionally contained EPA ± AA. Mean EPA and AA doses include zero values from trials not supplementing with EPA or AA.

[14] Four intervention arms in 3 trials contained AA, with doses ranging from 15 to 220 mg/d (45, 70) and 1.7%FA (55).

[15] Excluding 3 trials not reporting doses in %FA: *1*) baby food: 130 mg DHA, 4.5 mg EPA, 88 mg AA (47); *2*) fish oil: 276 mg DHA, 100 mg EPA, 0 mg AA (60); *3*) formula: 6.9 mg DHA/L, 0 mg EPA/L, 6.9 mg AA/L (29).

[16] Reflects outcomes pooled in meta-analysis. Because several trials evaluated multiple outcomes, the sum of outcomes is larger than the total number of trials. Studies were eligible for inclusion if the outcomes reported were in age-standardized units for cognition including from BSID (MDI, PDI), and IQ scores; or for visual acuity including from cycles/degree or logMAR. For 2 trials using the third edition of BSID, we calculated MDI from the weighted average of reported cognitive and language composite scores, and PDI from the BSID-III motor facet (see Supplemental Methods 2). Four trials (25, 41, 43, 56) reported other infant development outcomes (e.g., overall developmental quotient as reported by Griffiths Mental Development Scale, Knobloch, Passamanick, and Sherrads Developmental Screening Index, and Brunet-Lezine), which were too few and variable to perform a meta-analysis; study details for these 4 trials are included in Supplemental Tables 1 and 3.

[17] The K-ABC MPC standard score was considered as a measure of overall IQ in the meta-analysis. The MPC is a global measure of cognitive ability and is considered similar to IQ (35).

[18] Reporting results either in cycles/degree or in logMAR.

[19] Dropout for each trial was calculated as the average of dropout in intervention and control arms, for the latest age of outcome assessment. If multiple outcomes were reported at the same age, the smallest sample size was used here. The dropout data here exclude 4 trials (36, 50, 57, 69) that reported only analysis sample size, not initial sample size.

[20] Assessed using the Cochrane Risk of Bias tool (21). Each of 6 criteria (excluding the "other bias" criterion; see Supplemental Table 1) was scored as low (+1), high (–1), or unclear (0) risk of bias; these values were summed to generate an overall quality score.

although trials were also included from Bangladesh, China, Taiwan, Mexico, and Chile. Most Western trials evaluated predominantly white participants, although 4 US trials were conducted in predominantly (>60%) black participants. Among 24 trials reporting sufficient data to determine average maternal education, 11 evaluated populations with higher education (some college), 8 evaluated populations with average education (classified as mothers completing high school), and 5 evaluated populations with low education (less than high school). Among all trials, the average dropout between enrollment and outcome assessment was 33%. The mean ± SD study quality score was 3.2 ± 1.5, out of a possible range of –6 to + 6.

Among maternal supplementation trials, mean ± SD baseline maternal age was 29.4 ± 3.2 y, supplementation duration was 21.7 ± 7.5 wk, and DHA and EPA doses were 673 ± 547 and 297 ± 512 mg/d, respectively. Among preterm infant supplementation trials, mean ± SD age was 30.7 ± 2.2 wk gestation, supplementation duration was 45.3 ± 14.5 wk, and DHA, EPA, and AA doses were 0.28 ± 0.13, 0.12 ± 0.21, and 0.34 ± 0.28%FA, respectively. Among term-infant supplementation trials, most (72%) started supplementation within 1 wk of birth; the remainder (28%) started after weaning from breast milk. Mean ± SD supplementation duration was 37.2 ± 14.5 wk, and DHA, EPA, and AA doses were 0.38 ± 0.22, 0.05 ± 0.14, and 0.40 ± 0.29%FA, respectively. Across all trials, participants in control groups were provided either vegetable oil or standard formula/food.

Effects of n–3 PUFA supplementation on BSID. Twenty-one trials including 32 intervention arms reported on MDI and PDI, assessed in children at age 6–30 mo (median: 18 mo). When we explored different periods of supplementation, MDI was significantly improved by supplementation in preterm infants (3.33; 95% CI: 0.72, 5.93) (**Figure 1**). Compared with maternal supplementation, the benefit on MDI was significantly larger in preterm infants (*P*-interaction = 0.018) (**Supplemental Table 5**). For PDI, no significant effect was seen for analyses stratified by intervention period (**Figure 2**).

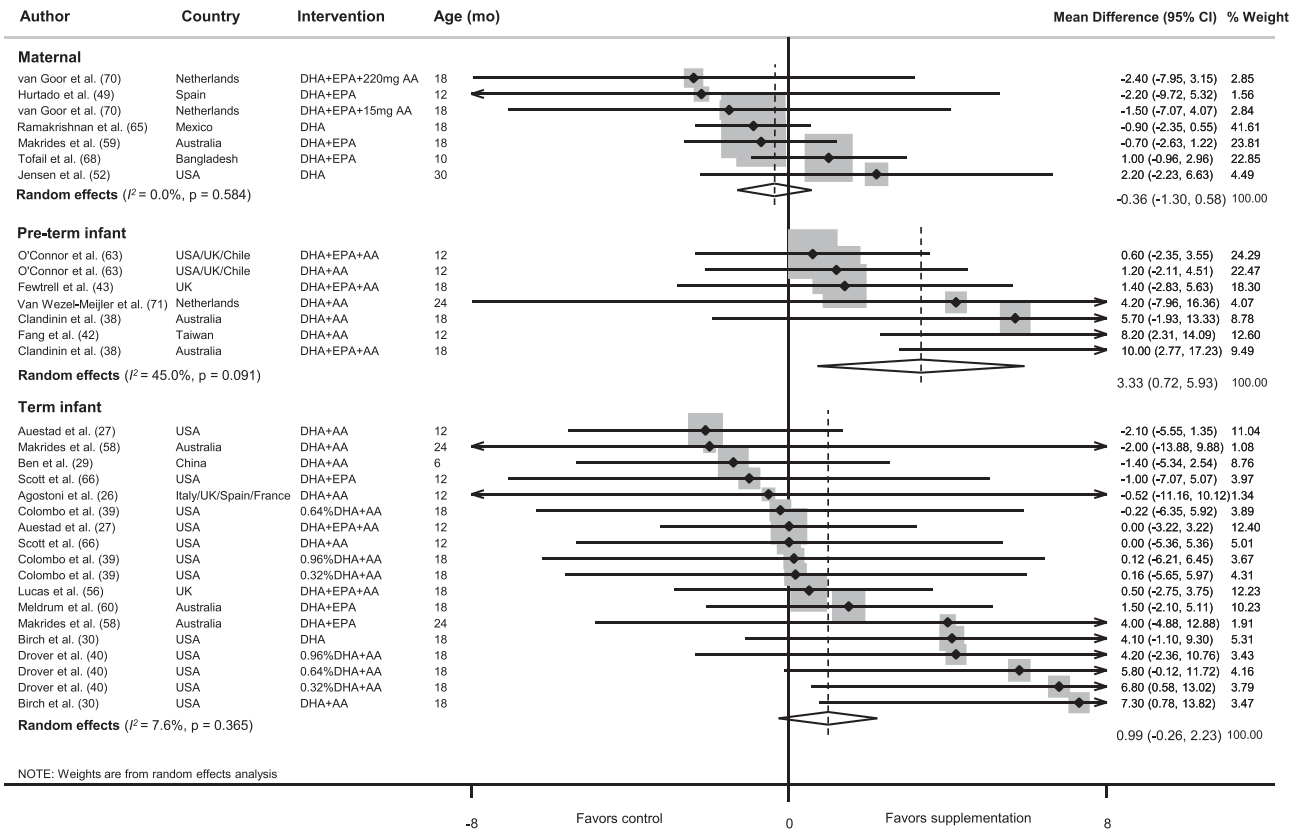

FIGURE 1 Effects of n–3 PUFA supplementation on Bayley Scales of Infant Development mental developmental index (weighted mean difference) in randomized controlled trials. These analyses included 32 intervention arms from 21 trials, with an overall pooled result across all supplementation periods of 0.91 (95% CI: 0.00, 1.81; $I^2 = 27.0\%$). Significant differences were seen by intervention period, with stronger effects for supplementation in preterm infants, compared with maternal supplementation (P-interaction = 0.018). Findings were pooled using random-effects meta-analysis. Shaded squares represent the weight of each study, and dotted vertical lines and diamonds represent the pooled central estimate and its 95% CI, respectively, for each group. AA, arachidonic acid.

In our main pooled analyses across all supplementation periods, n–3 PUFA supplementation increased both MDI (0.91 higher index; 95% CI: 0.005, 1.81; $P = 0.049$) and PDI (1.06; 95% CI: 0.10, 2.03; $P = 0.031$) (see Figures 1 and 2 legends). Results were not appreciably altered after excluding 2 trials (59, 60) using the third edition of BSID (MDI: 1.08; 95% CI: 0.08, 2.08; $P = 0.034$; PDI: 1.10; 95% CI: –0.01, 2.20; $P = 0.052$); or by excluding one trial in infants diagnosed with phenylketonuria (26) (MDI: 0.94; 95% CI: 0.02, 1.85; $P = 0.046$; PDI: 1.13; 95% CI: 0.16, 2.09; $P = 0.022$). Heterogeneity was low to moderate (MDI: $I^2 = 27\%$; PDI: $I^2 = 42.3\%$).

Effects of n–3 PUFA supplementation on IQ. Only 7 trials with 9 intervention arms reported on IQ, measured in children aged 3–12 y (median: 5.8 y). No significant effects on IQ were identified when we explored each supplementation period separately (**Figure 3**), or in our main pooled analyses across all supplementation periods (0.20; 95% CI: –1.56, 1.96; $P = 0.83$; Figure 3 legend).

Effects of n–3 PUFA supplementation on visual acuity. Twenty-four trials including 35 intervention arms reported effects on visual acuity, tested in children aged between 2 and 64 mo (median: 12 mo). When we explored effects stratified by intervention period, benefits were evident in both preterm (–0.08 logMAR; 95% CI: –0.14, –0.01) and term infants (–0.08 logMAR; 95% CI: –0.11, –0.05), with a nonsignificant trend for maternal supplementation (–0.02 logMAR; 95% CI: –0.04, 0.00) (**Figure 4**). Comparing these differences, benefits were significantly larger for supplementation in term infants compared with maternal supplementation (P-interaction = 0.022).

In our main pooled analysis across all supplementation periods, n–3 PUFA supplementation improved visual acuity by –0.063 logMAR (95% CI: –0.084, –0.041; $P < 0.001$; Figure 4 legend). Observed heterogeneity was high ($I^2 = 81.6\%$). In post hoc analysis, a more robust effect was seen in children in trials using VEP compared with behavioral visual acuity measures (P-interaction = 0.010).

Subgroup analyses. We did not identify statistically significant differences in any findings according to world region, race, maternal education, age at outcome assessment, supplementation duration, DHA or EPA dose, DHA: AA ratio, or quality score (P-interaction > 0.05 each) (**Supplemental Table 5**). We could not assess heterogeneity by type of placebo due to insufficient variability across trials.

Publication bias. Based on visual inspection of funnel plots and Egger's tests (**Supplemental Figure 2**), there was evidence for potential publication bias for MDI (Egger's test $P = 0.005$). Duval and Tweedie's trim-and-fill method suggested that an adjusted meta-analysis including 7 hypothetically missing small studies would result in an absence of significant effects on MDI (0.17; 95% CI: –0.90, 1.23).

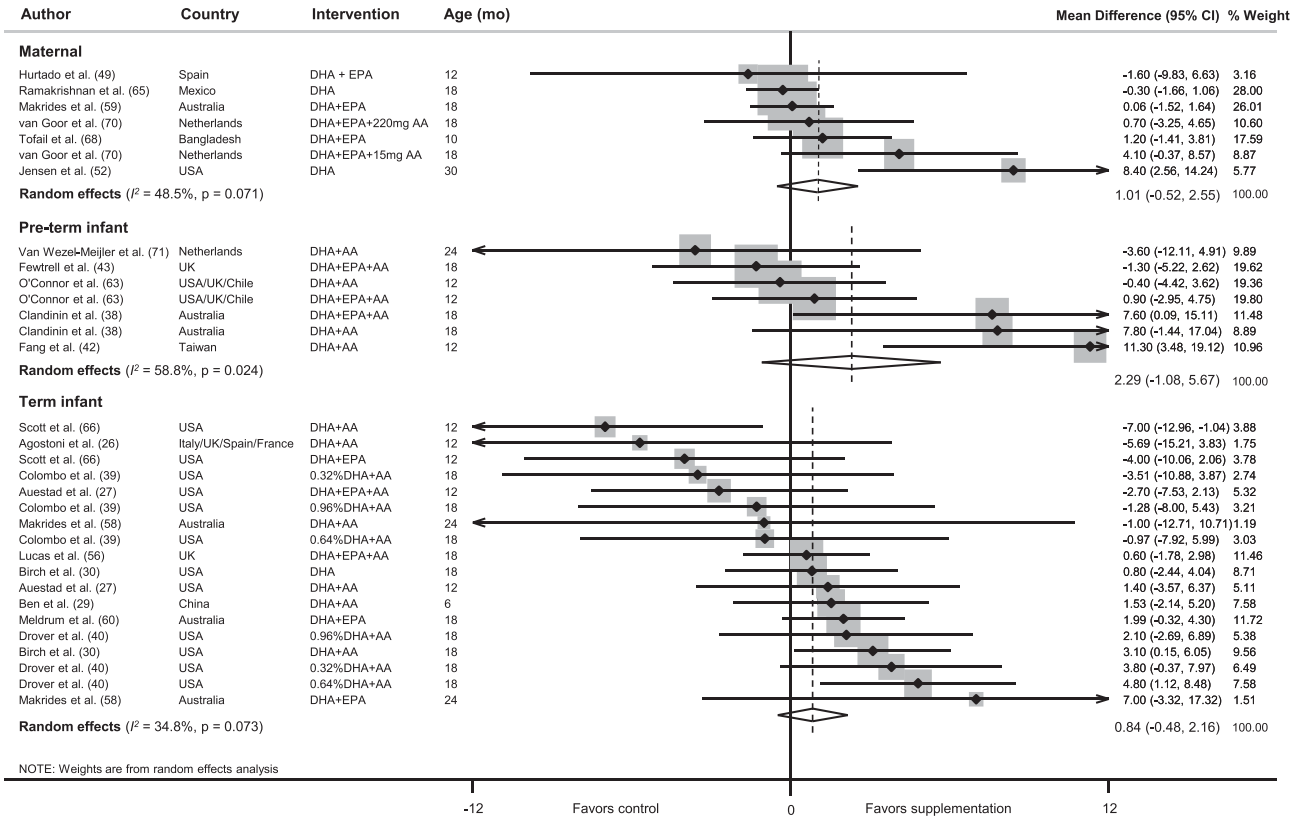

FIGURE 2 Effects of n–3 PUFA supplementation on Bayley Scales of Infant Development psychomotor developmental index (weighted mean difference) in randomized controlled trials. These analyses included 32 intervention arms from 21 trials, with an overall pooled result across all supplementation periods of 1.06 (95%CI: 0.10, 2.03; I^2 = 42.3%). Observed potential differences by intervention period did not achieve statistical significance (*P*-interaction > 0.05). Findings were pooled using random-effects meta-analysis. Shaded squares represent the weight of each study, and dotted vertical lines and diamonds represent the pooled central estimate and its 95% CI, respectively, for each group. AA, arachidonic acid.

Given evidence for strongest MDI effects in preterm infants, we re-evaluated publication bias excluding maternal and infant studies. When restricted to studies of preterm infants, Egger's test was borderline (P = 0.047), and trim-and-fill methods suggested that an adjusted meta-analysis including 3 hypothetically missing studies would result in no significant effect on MDI (1.20; 95% CI: –1.80, 4.19). All other outcomes (PDI, IQ, visual acuity) did not demonstrate evidence of publication bias.

Discussion

This systematic review and meta-analysis of 38 trials including 53 interventions arms across critical periods of brain development—from pregnancy through infancy—demonstrated a significant benefit of n–3 PUFA supplementation on infant cognitive development and visual acuity. Visual acuity showed the strongest benefit, followed by BSID PDI. Benefits were also seen for BSID MDI, but with statistical evidence for potential publication bias. No significant association was found for overall childhood IQ, though the IQ analysis was limited by the small number of studies. We also identified evidence for potentially greater benefits of n–3 PUFA supplementation in both preterm and term infants for visual acuity; and in preterm infants for MDI. These novel findings provide, to our knowledge, the most complete accounting of evidence for potential benefits of n–3 PUFA supplementation on cognitive development in randomized trials.

The brain develops meaningfully from the last trimester of pregnancy through the first 2 y of life. Although the intervention groups in our investigation (mothers, preterm infants, term infants) have important differences, each of these time periods targets the developing brain. Thus, our pooled findings can be considered at least an exploratory summary estimate of the effect of such interventions across the broad period of early brain development. The observed greater benefit on visual acuity with supplementation after birth is consistent with the timing of retinal and visual cortex neurodevelopment, much of which occurs postnatally (73). This may explain why infant supplementation produced larger improvements in visual acuity than maternal supplementation. Whereas stronger benefits for MDI of supplementation in preterm infants could partly relate to publication bias, this could also be attributable to larger baseline DHA deficiencies in this population; and also potentially to the greater importance of DHA for this cognitive outcome in the last weeks of development that normally occur in utero. Compared to term infants, preterm infants can have both greater nutrient demands to support rapid growth and more limited supply of n–3 PUFAs, given that most prenatal DHA accumulation in the brain occurs during the last trimester (1). Thus, supplementation during early infancy may restore n–3 PUFA concentrations toward concentrations seen in term infants, lending a possible explanation to the greater benefit on mental development demonstrated in preterm infants. Our findings suggested this could also be true for psychomotor development, although this difference was not statistically significant.

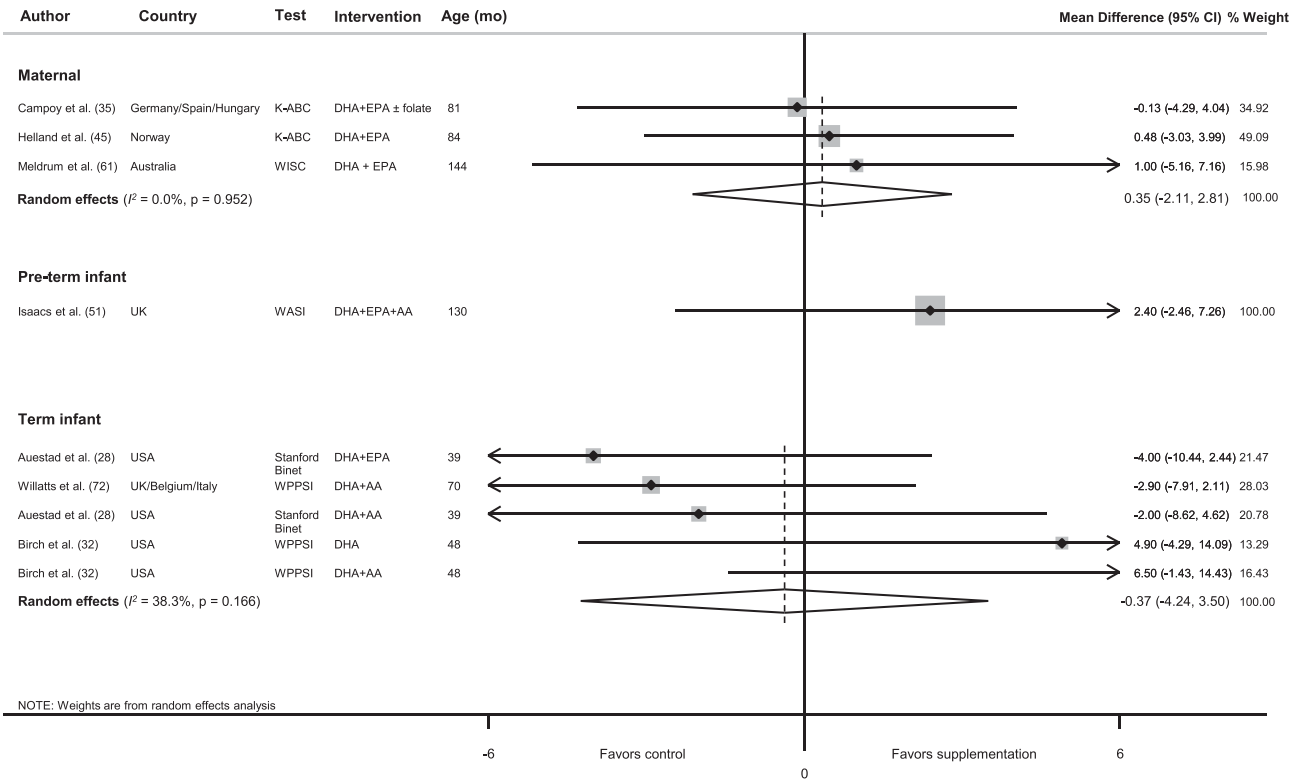

FIGURE 3 Effects of n–3 PUFA supplementation on intelligence quotient (weighted mean difference) in randomized controlled trials. These analyses included 9 intervention arms from 7 trials, with an overall pooled result across all supplementation periods of 0.20 (95% CI: –1.56, 1.96; $I^2 = 0.0\%$). No statistically significant differences were identified by intervention period (P-interaction > 0.05 each). Subgroup meta-analysis was not performed for preterm infants given that only one trial was identified, shown here. Other findings were pooled using random-effects meta-analysis. Shaded squares represent the weight of each study, and dotted vertical lines and diamonds represent the pooled central estimate and its 95% CI, respectively, for each group. AA, arachidonic acid; K-ABC, Kaufman Assessment Battery for Children; WASI, Wechsler Abbreviated Scale of Intelligence; WISC, Wechsler Intelligence Scale for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence.

Based on a much smaller number of trials, we did not identify any significant effects on global intelligence in later childhood. Most trials focused on well-tested, age-standardized measures of specific developmental indices, rather than IQ. It is possible that n–3 PUFA supplements benefit only specific cognitive domains, such as reflected by PDI and visual acuity, which might not be reflected in an improved IQ score that integrates performance across diverse domains varying in vulnerability to low PUFA. In this case, a global IQ measure may not be sufficiently sensitive to effects of n–3 PUFAs, which could play more critical roles in specific brain areas and functions such as memory or executive function. If so, the potential long-term advantages of better neurodevelopment at earlier ages may need to be evaluated in other ways, for example in terms of academic achievement, social success, or other development landmarks. Finally, focusing on group mean values of global intelligence may be less sensitive to interventions than measuring shifts in cognitive distributions: e.g., n–3 PUFAs could significantly reduce the proportions of children with suboptimal development below a certain threshold, which may be more sensitive and relevant for population health than group mean values. For example, in 2 trials of n–3 PUFA supplementation which evaluated neurodevelopmental endpoints (e.g., visual acuity, various BSID endpoints) according to proportions of children with scores below a threshold, n–3 PUFA supplementation significantly lowered risk, despite no significant differences in mean scores in these trials (59, 74). Observational investigations of maternal fish consumption further support this concept that effects of dietary n–3 PUFAs may be more relevant for reducing proportions of children with suboptimal outcomes than altering population means (8). Effects on prevalence of suboptimal outcomes were not reported in most trials and thus could not be evaluated in the present meta-analysis. Our results support the need for additional studies, including reanalysis of existing trial results by their investigators, to consider such outcomes.

Prior studies. Our findings build upon and substantially extend prior work in this area. Several prior meta-analyses evaluated only one period of supplementation, limiting statistical power. A 2013 meta-analysis restricting to maternal supplementation pooled 7 trials stratified by age of assessment in childhood, with at most 2 trials in each subgroup (12). The authors identified higher cognitive scores in 2- to 5-y-old children (based on 2 trials), with no statistically significant effects in other subgroups. In another meta-analysis of maternal supplementation only, no significant effects were seen on any neurodevelopmental outcome after age 2, yet the largest pooled analysis in this prior study included only 3 trials, and most assessments were of single trials (19). A meta-analysis restricted to supplementation of preterm infants did not detect significant effects on PDI or MDI, but was based on pooling of only 4 trials; meta-analysis of visual acuity was not performed (16). Similarly, a prior meta-analysis restricted to supplementation of term infants detected no significant effects on PDI or MDI; meta-analysis of visual acuity was not performed (17) Consistent with our present results, in a meta-analysis focused on visual acuity in trials of

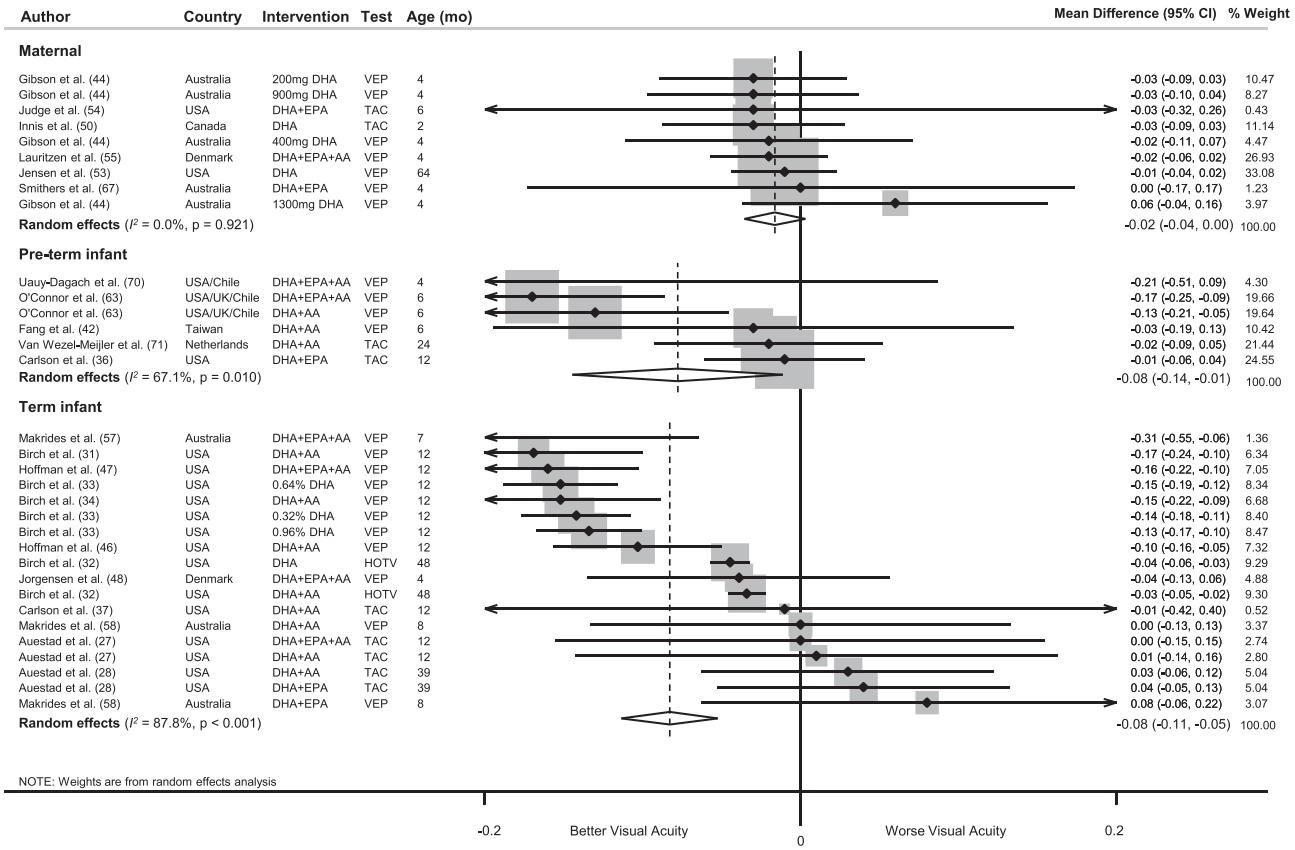

FIGURE 4 Effects of n–3 PUFA supplementation on visual acuity (weighted mean difference) in randomized controlled trials. These analyses included 35 intervention arms from 24 trials, with an overall pooled result across all supplementation periods of –0.06 (95%CI: –0.08, –0.04; I^2 = 81.6%). Stronger effects were identified for supplementation in term infants, compared with maternal supplementation (*P*-interaction = 0.022), but were not significantly higher in preterm infants (*P*-interaction = 0.115). Findings were pooled using random-effects meta-analysis. AA, arachidonic acid; HOTV, distance visual acuity testing using HOTV optotypes chart; TAC, Teller Acuity Card; VEP, Visual Evoked Potential.

infant supplementation, n–3 PUFA supplementation improved VEP at 12 months (weighted mean difference: –0.11; 95% CI: –0.20, –0.03) (15). Our investigation extends each of these prior studies by pooling additional measures of visual acuity and IQ, including follow-up for visual acuity beyond 12 mo of age, and evaluating the effects of n–3 PUFA supplementation in mothers, preterm infants, and term infants. This allowed confirmation and quantification of benefits of supplementation on visual acuity in both term and preterm infants; and of benefits on PDI, which appeared generally similar by supplementation period in our investigation but may have been missed due to limited power if the different periods were only evaluated separately.

Strengths/limitations. Our investigation has several strengths. Our comprehensive search of multiple databases makes it unlikely that major studies were missed, while our duplicate inclusion decisions and data extractions reduce the possibility of errors or bias. We focused on randomized controlled trials, providing direct inference on causal effects of n–3 PUFA supplementation. We evaluated multiple periods of supplementation and cognitive outcomes, providing a comprehensive picture of the present evidence in this field. Heterogeneity, study quality, and potential publication bias were evaluated using quantitative methods.

Potential limitations should be considered. Relatively high loss to follow-up was seen in many trials, reducing statistical power, although the generally similar drop-out rates between n–3 PUFA and placebo arms would minimize threats to validity. Few studies evaluated global intelligence later in childhood, limiting power to assess this outcome. DHA supplementation could be especially relevant in women or infants with relative deficiency, yet neither baseline DHA status nor background dietary intakes were generally assessed in these trials. Our findings highlight the need for additional trials testing effects in deficient populations. Many trials focused on predominantly white, more educated women in high-income countries, and more studies are needed in other maternal and child populations. Most studies only reported differences in mean scores, and effects on the proportion of children below a certain threshold may be more sensitive and clinically relevant (59, 74).

In conclusion, this systematic review and meta-analysis identified significant benefits of n–3 PUFA supplementation on psychomotor development and visual acuity, with potentially stronger effects in preterm and term infants compared to maternal supplementation. We found more equivocal findings for MDI and no significant effects on global IQ later in childhood. Together with observational studies of maternal fish consumption, these findings support benefits of n–3 PUFA on psychomotor and visual acuity development during pregnancy and the first 2 y of life.

Acknowledgments

We thank Fumiaki Imamura at the University of Cambridge for useful comments and suggestions on statistical analysis. The authors' responsibilities were as follows— LP, DB, WF, CD, and

DM: study concept and design; MS, LP, and SK: acquisition, analysis, or interpretation of data; MS and DM: drafting of manuscript; all authors: critical revision of manuscript for important intellectual content; MS: statistical analysis; DM: obtained funding, study supervision; and all authors: read and approved the final version of this paper.

References

1. Uauy R, Dangour AD. Fat and fatty acid requirements and recommendations for infants of 0–2 years and children of 2–18 years. Ann Nutr Metab 2009;55:76–96.
2. Cheatham C. Omega-3 fatty acids and the development of cognitive abilities: a review of DHA supplementation studies. CAB Rev: Perspect Agricul Vet Sci Nutr Nat Resources 2008;3(001).
3. Nyaradi A, Li J, Hickling S, Foster J, Oddy WH. The role of nutrition in children's neurocognitive development, from pregnancy through childhood. Front Hum Neurosci 2013;7. doi: 10.1111/mcn.12015. [Epub ahead of print].
4. Brenna JT, Lapillonne A. Background paper on fat and fatty acid requirements during pregnancy and lactation. Ann Nutr Metab 2009;55:97–122.
5. Innis SM. Omega-3 Fatty acids and neural development to 2 years of age: do we know enough for dietary recommendations? J Pediatr Gastroenterol Nutrition 2009;48 Suppl 1:S16–24.
6. McCann JC, Ames BN. Is docosahexaenoic acid, an n–3 long-chain polyunsaturated fatty acid, required for development of normal brain function? An overview of evidence from cognitive and behavioral tests in humans and animals. Am J Clin Nutr 2005;82:281–95.
7. Micha R, Khatibzadeh S, Shi P, Fahimi S, Lim S, Andrews KG, Engell RE, Powles J, Ezzati M, Mozaffarian D, et al. Global, regional, and national consumption levels of dietary fats and oils in 1990 and 2010: a systematic analysis including 266 country-specific nutrition surveys. BMJ 2014;348:g2272.
8. Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, Golding J. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet 2007;369:578–85.
9. Oken E, Radesky JS, Wright RO, Bellinger DC, Amarasiriwardena CJ, Kleinman KP, Hu H, Gillman MW. Maternal fish intake during pregnancy, blood mercury levels, and child cognition at age 3 years in a US cohort. Am J Epidemiol 2008;167:1171–81.
10. Farquharson J, Cockburn F, Patrick WA, Jamieson EC, Logan RW. Infant cerebral cortex phospholipid fatty-acid composition and diet. Lancet 1992;340:810–3.
11. Makrides M, Neumann MA, Byard RW, Simmer K, Gibson RA. Fatty acid composition of brain, retina, and erythrocytes in breast- and formula-fed infants. Am J Clin Nutr 1994;60:189–94.
12. Gould JF, Smithers LG, Makrides M. The effect of maternal omega-3 (n–3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2013;97:531–44.
13. Jiao J, Li Q, Chu J, Zeng W, Yang M, Zhu S. Effect of n–3 PUFA supplementation on cognitive function throughout the life span from infancy to old age: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2014;100:1422–36.
14. Qawasmi A, Landeros-Weisenberger A, Leckman JF, Bloch MH. Meta-analysis of long-chain polyunsaturated fatty acid supplementation of formula and infant cognition. Pediatrics 2012;129:1141–9.
15. Qawasmi A, Landeros-Weisenberger A, Bloch MH. Meta-analysis of LCPUFA supplementation of infant formula and visual acuity. Pediatrics 2013;131:e262–72.
16. Schulzke SM, Patole SK, Simmer K. Long-chain polyunsaturated fatty acid supplementation in preterm infants. Cochrane Database Syst Rev 2011:CD000375.
17. Simmer K, Patole SK, Rao SC. Long-chain polyunsaturated fatty acid supplementation in infants born at term. Cochrane Database Syst Rev 2011:CD000376.
18. Smithers LG, Gibson RA, McPhee A, Makrides M. Effect of long-chain polyunsaturated fatty acid supplementation of preterm infants on disease risk and neurodevelopment: a systematic review of randomized controlled trials. Am J Clin Nutr 2008;87:912–20.
19. Delgado-Noguera MF, Calvache JA, Bonfill Cosp X, Kotanidou EP, Galli-Tsinopoulou A. Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development. Cochrane Database Syst Rev 2015;7:CD007901.
20. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
21. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org.
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
24. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.
25. Agostoni C, Trojan S, Bellu R, Riva E, Bruzzese MG, Giovannini M. Developmental quotient at 24 months and fatty acid composition of diet in early infancy: a follow up study. Arch Dis Child 1997;76:421–4.
26. Agostoni C, Harvie A, McCulloch DL, Demellweek C, Cockburn F, Giovannini M, Murray G, Harkness RA, Riva E. A randomized trial of long-chain polyunsaturated fatty acid supplementation in infants with phenylketonuria. Dev Med Child Neurol 2006;48:207–12.
27. Auestad N, Halter R, Hall RT, Blatter M, Bogle ML, Burks W, Erickson JR, Fitzgerald KM, Dobson V, Innis SM, et al. Growth and development in term infants fed long-chain polyunsaturated fatty acids: a double-masked, randomized, parallel, prospective, multivariate study. Pediatrics 2001;108:372–81.
28. Auestad N, Scott DT, Janowsky JS, Jacobsen C, Carroll RE, Montalto MB, Halter R, Qiu W, Jacobs JR, Connor WE, et al. Visual, cognitive, and language assessments at 39 months: a follow-up study of children fed formulas containing long-chain polyunsaturated fatty acids to 1 year of age. Pediatrics 2003;112(3 Pt 1):e177–83.
29. Ben XM, Zhou XY, Zhao WH, Yu WL, Pan W, Zhang WL, Wu SM, Van Beusekom CM, Schaafsma A. Growth and development of term infants fed with milk with long-chain polyunsaturated fatty acid supplementation. Chin Med J (Engl) 2004;117:1268–70.
30. Birch EE, Garfield S, Hoffman DR, Uauy R, Birch DG. A randomized controlled trial of early dietary supply of long-chain polyunsaturated fatty acids and mental development in term infants. Dev Med Child Neurol 2000;42:174–81.
31. Birch EE, Castaneda YS, Wheaton DH, Birch DG, Uauy RD, Hoffman DR. Visual maturation of term infants fed long-chain polyunsaturated fatty acid-supplemented or control formula for 12 mo. Am J Clin Nutr 2005;81:871–9.
32. Birch EE, Garfield S, Castaneda Y, Hughbanks-Wheaton D, Uauy R, Hoffman D. 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. Early Hum Dev 2007;83:279–84.
33. Birch EE, Carlson SE, Hoffman DR, Fitzgerald-Gustafson KM, Fu VL, Drover JR, Castaneda YS, Minns L, Wheaton DK, Mundy D, et al. The DIAMOND (DHA Intake And Measurement Of Neural Development) study: a double-masked, randomized controlled clinical trial of the maturation of infant visual acuity as a function of the dietary level of docosahexaenoic acid. Am J Clin Nutr 2010;91:848–59.
34. Birch EE, Hoffman DR, Castaneda YS, Fawcett SL, Birch DG, Uauy RD. A randomized controlled trial of long-chain polyunsaturated fatty acid supplementation of formula in term infants after weaning at 6 wk of age. Am J Clin Nutr 2002;75:570–80.
35. Campoy C, Escolano-Margarit MV, Ramos R, Parrilla-Roure M, Csabi G, Beyer J, Ramirez-Tortosa MC, Molloy AM, Decsi T, Koletzko BV. Effects of prenatal fish-oil and 5-methyltetrahydrofolate supplementation on cognitive development of children at 6.5 y of age. Am J Clin Nutr 2011;94(6 Suppl):S1880–8.
36. Carlson SE, Werkman SH, Rhodes PG, Tolley EA. Visual-acuity development in healthy preterm infants: effect of marine-oil supplementation. Am J Clin Nutr 1993;58:35–42.
37. Carlson SE, Ford AJ, Werkman SH, Peeples JM, Koo WW. Visual acuity and fatty acid status of term infants fed human milk and formulas with and without docosahexaenoate and arachidonate from egg yolk lecithin. Pediatr Res 1996;39:882–8.

38. Clandinin MT, Van Aerde JE, Merkel KL, Harris CL, Springer MA, Hansen JW, Diersen-Schade DA. Growth and development of preterm infants fed infant formulas containing docosahexaenoic acid and arachidonic acid. J Pediatr 2005;146:461–8.
39. Colombo J, Carlson SE, Cheatham CL, Shaddy DJ, Kerling EH, Thodosoff JM, Gustafson KM, Brez C. Long-term effects of LCPUFA supplementation on childhood cognitive outcomes. Am J Clin Nutr 2013;98:403–12.
40. Drover JR, Hoffman DR, Castaneda YS, Morale SE, Garfield S, Wheaton DH, Birch EE. Cognitive function in 18-month-old term infants of the DIAMOND study: a randomized, controlled clinical trial with multiple dietary levels of docosahexaenoic acid. Early Hum Dev 2011;87:223–30.
41. Dunstan JA, Simmer K, Dixon G, Prescott SL. Cognitive assessment of children at age 2(1/2) years after maternal fish oil supplementation in pregnancy: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2008;93:F45–50. doi: 10.1136/adc.2006.099085.
42. Fang PC, Kuo HK, Huang CB, Ko TY, Chen CC, Chung MY. The effect of supplementation of docosahexaenoic acid and arachidonic acid on visual acuity and neurodevelopment in larger preterm infants. Chang Gung Med J 2005;28:708–15.
43. Fewtrell MS, Abbott RA, Kennedy K, Singhal A, Morley R, Caine E, Jamieson C, Cockburn F, Lucas A. Randomized, double-blind trial of long-chain polyunsaturated fatty acid supplementation with fish oil and borage oil in preterm infants. J Pediatr 2004;144:471–9. doi: 10.1016/j.jpeds.2004.01.034.
44. Gibson RA, Neumann MA, Makrides M. Effect of increasing breast milk docosahexaenoic acid on plasma and erythrocyte phospholipid fatty acids and neural indices of exclusively breast fed infants. Eur J Clin Nutr 1997;51:578–84.
45. Helland IB, Smith L, Blomen B, Saarem K, Saugstad OD, Drevon CA. 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. Pediatrics 2008;122:e472–9.
46. Hoffman DR, Birch EE, Castaneda YS, Fawcett SL, Wheaton DH, Birch DG, Uauy R. Visual function in breast-fed term infants weaned to formula with or without long-chain polyunsaturates at 4 to 6 months: a randomized clinical trial. J Pediatr 2003;142:669–77.
47. Hoffman DR, Theuer RC, Castaneda YS, Wheaton DH, Bosworth RG, O'Connor AR, Morale SE, Wiedemann LE, Birch EE. Maturation of visual acuity is accelerated in breast-fed term infants fed baby food containing DHA-enriched egg yolk. J Nutr 2004;134:2307–13.
48. Horby Jorgensen M, Holmer G, Lund P, Hernell O, Michaelsen KF. Effect of formula supplemented with docosahexaenoic acid and gamma-linolenic acid on fatty acid status and visual acuity in term infants. J Pediatr Gastroenterol Nutr 1998;26:412–21.
49. Hurtado JA, Iznaola C, Pena M, Ruiz J, Pena-Quintana L, Kajarabille N, Rodriguez-Santana Y, Sanjurjo P, Aldamiz-Echevarria L, Ochoa J, et al. Effects of maternal omega-3 supplementation on fatty acids and on visual and cognitive development. J Pediatr Gastroenterol Nutr 2015;61:472–80.
50. Innis SM, Friesen RW. Essential n–3 fatty acids in pregnant women and early visual acuity maturation in term infants. Am J Clin Nutr 2008;87:548–57.
51. Isaacs EB, Ross S, Kennedy K, Weaver LT, Lucas A, Fewtrell MS. 10-year cognition in preterms after random assignment to fatty acid supplementation in infancy. Pediatrics 2011;128:e890–8.
52. Jensen CL, Voigt RG, Prager TC, Zou YL, Fraley JK, Rozelle JC, Turcich MR, Llorente AM, Anderson RE, Heird WC. Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants. Am J Clin Nutr 2005;82:125–32.
53. Jensen CL, Voigt RG, Llorente AM, Peters SU, Prager TC, Zou YL, Rozelle JC, Turcich MR, Fraley JK, Anderson RE, et al. Effects of early maternal docosahexaenoic acid intake on neuropsychological status and visual acuity at five years of age of breast-fed term infants. J Pediatr 2010;157:900–5.
54. Judge MP, Harel O, Lammi-Keefe CJ. A docosahexaenoic acid-functional food during pregnancy benefits infant visual acuity at four but not six months of age. Lipids 2007;42:117–22.
55. Lauritzen L, Jorgensen MH, Mikkelsen TB, Skovgaard l M, Straarup EM, Olsen SF, Hoy CE, Michaelsen KF. Maternal fish oil supplementation in lactation: effect on visual acuity and n–3 fatty acid content of infant erythrocytes. Lipids 2004;39:195–206.
56. Lucas A, Stafford M, Morley R, Abbott R, Stephenson T, MacFadyen U, Elias-Jones A, Clements H. Efficacy and safety of long-chain polyunsaturated fatty acid supplementation of infant-formula milk: a randomised trial. Lancet 1999;354:1948–54.
57. Makrides M, Neumann M, Simmer K, Pater J, Gibson R. Are long-chain polyunsaturated fatty acids essential nutrients in infancy? Lancet 1995;345:1463–8.
58. Makrides M, Neumann MA, Simmer K, Gibson RA. A critical appraisal of the role of dietary long-chain polyunsaturated fatty acids on neural indices of term infants: a randomized, controlled trial. Pediatrics 2000;105(1 Pt 1):32–8.
59. Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. JAMA 2010;304:1675–83.
60. Meldrum SJ, D'Vaz N, Simmer K, Dunstan JA, Hird K, Prescott SL. Effects of high-dose fish oil supplementation during early infancy on neurodevelopment and language: a randomised controlled trial. Br J Nutr 2012;108:1443–54.
61. Meldrum S, Dunstan JA, Foster JK, Simmer K, Prescott SL. Maternal fish oil supplementation in pregnancy: a 12 year follow-up of a randomised controlled trial. Nutrients 2015;7:2061–7.
62. Muthayya S, Eilander A, Transler C, Thomas T, Knaap HC, Srinivasan K, Klinken BJ, Osendarp SJ, Kurpad AV. 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. Am J Clin Nutr 2009;89:1766–75.
63. O'Connor DL, Hall R, Adamkin D, Auestad N, Castillo M, Connor WE, Connor SL, Fitzgerald K, Groh-Wargo S, Hartmann EE, et al. Growth and development in preterm infants fed long-chain polyunsaturated fatty acids: a prospective, randomized controlled trial. Pediatrics 2001;108:359–71.
64. Osendarp SJ, Baghurst KI, Bryan J, Calvaresi E, Hughes D, Hussaini M, Karyadi SJ, Klinken BJ, Knaap HC, Lukito W, et al. 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. Am J Clin Nutr 2007;86:1082–93.
65. Ramakrishnan U, Stinger A, DiGirolamo AM, Martorell R, Neufeld LM, Rivera JA, Schnaas L, Stein AD, Wang M. Prenatal docosahexaenoic acid supplementation and offspring development at 18 months: randomized controlled trial. PLoS One 2015;10:e0120065.
66. Scott DT, Janowsky JS, Carroll RE, Taylor JA, Auestad N, Montalto MB. Formula supplementation with long-chain polyunsaturated fatty acids: are there developmental benefits? Pediatrics 1998;102:E59.
67. Smithers LG, Gibson RA, Makrides M. Maternal supplementation with docosahexaenoic acid during pregnancy does not affect early visual development in the infant: a randomized controlled trial. Am J Clin Nutr 2011;93:1293–9.
68. Tofail F, Kabir I, Hamadani JD, Chowdhury F, Yesmin S, Mehreen F, Huda SN. Supplementation of fish-oil and soy-oil during pregnancy and psychomotor development of infants. J Health Popul Nutr 2006;24:48–56.
69. Uauy-Dagach R, Mena P, Hoffman DR. Essential fatty acid metabolism and requirements for LBW infants. Acta Paediatr Suppl 1994;405:78–85.
70. van Goor SA, Dijck-Brouwer DA, Erwich JJ, Schaafsma A, Hadders-Algra M. The influence of supplemental docosahexaenoic and arachidonic acids during pregnancy and lactation on neurodevelopment at eighteen months. Prostaglandins Leukot Essent Fatty Acids 2011;84:139–46.
71. van Wezel-Meijler G, van der Knaap MS, Huisman J, Jonkman EJ, Valk J, Lafeber HN. Dietary supplementation of long-chain polyunsaturated fatty acids in preterm infants: effects on cerebral maturation. Acta Paediatr 2002;91:942–50.
72. Willatts P, Forsyth S, Agostoni C, Casaer P, Riva E, Boehm G. Effects of long-chain PUFA supplementation in infant formula on cognitive function in later childhood. Am J Clin Nutr 2013;98:S536–42.
73. Wiesel TN. Postnatal development of the visual cortex and the influence of environment. Nature 1982;299:583–91.
74. Mulder KA, King DJ, Innis SM. Omega-3 fatty acid deficiency in infants before birth identified using a randomized trial of maternal DHA supplementation in pregnancy. PLoS One 2014;9:e83764.