Citations in the main paper include: (1-74)

**Supplemental Methods 1. Search Strategy**

We performed searches of electronic databases including PubMed ([www.ncbi.nlm.nih.go/pubmed](http://www.ncbi.nlm.nih.go/pubmed)), PsycINFO (<http://search.proquest.com/psycinfo>), EMBASE ([www.ovid.com/embase](http://www.ovid.com/embase)), and The Cochrane library ([www.thecochranelibrary.com](http://www.thecochranelibrary.com)) for relevant articles from the earliest indexing year through June 1, 2015, without language restrictions. We updated the search through April 14, 2016, in PubMed, the database identifying nearly all prior articles; as well as adding searches in clinicaltrials.gov for additional publications and ongoing trials.

**PubMed search terms**

“fatty acids, omega-3”[MeSH] OR “fatty acid”[tiab] OR “fatty acids”[tiab] OR “fatty-acid”[tiab] OR “fatty-acids”[tiab] OR “omega-3”[tiab] OR “n-3”[tiab] OR “DHA”[tiab] OR “docosahexaenoic acid”[tiab] OR “EPA”[tiab] OR “eicosapentaenoic acid”[tiab] OR “essential fatty acid” [tiab] OR “essential fatty acids” [tiab] OR “LCPUFA”[tiab] OR “long chain polyunsaturated” [tiab] OR “long-chain polyunsaturated” [tiab] OR “PUFA”[tiab] OR “PUFAs”[tiab] OR “polyunsaturated fatty acid”[tiab] OR “polyunsaturated fatty acids”[tiab] OR “fish oils”[MeSH] OR “fish oil”[tiab] OR “fish proteins”[MeSH] OR “fishes”[MeSH] OR “fish products”[MeSH] OR “fish”[tiab] OR “seafood”[MeSH] OR “seafood”[tiab]

**AND**

neurodevelopment\*[tiab] OR neurodevelopmental[tiab] OR “neural development"[tiab] OR “brain development”[tiab] OR “brain”[tiab] OR “neurological” [tiab] OR “cognitive development”[tiab] OR “cognition”[MeSH] OR “cognition”[tiab] OR “cognitive”[tiab] OR “mental development”[tiab] OR “psychomotor development” [tiab] OR “language”[MeSH] OR “language”[tiab] OR “intelligence”[tiab] OR “mental processes” [MeSH] OR “learning”[tiab] OR “executive function”[tiab] OR “memory”[tiab] OR “focus”[tiab] OR “attention”[tiab] OR “mental”[tiab] OR “visual acuity”[MeSH] OR “visual acuity”[tiab] OR “vision”[tiab] OR “eye development”[tiab] or “visual development”[tiab] or “visual function”[tiab] OR “retina”[tiab] OR “behavior”[MeSH] OR “behavior and behavior mechanisms”[MeSH] OR behavior\*[tiab] OR behaviour\*[tiab] OR “anxiety”[tiab] OR “emotions”[MeSH] OR emotion\*[tiab] OR “emotional”[tiab] OR “mental health”[MeSH] OR “aggression”[tiab] OR “mood”[tiab] OR “psychosocial”[tiab] OR “depressive”[tiab] OR “developmental disabilities”[MeSH] OR “developmental disability”[tiab] OR “developmental delay”[tiab] OR “developmental delays”[tiab] OR “attention deficit”[tiab] OR “attention deficit and disruptive behavior disorders”[MeSH] OR “ADHD”[tiab] OR “autism”[tiab] OR "autistic"[tiab] OR “autistic disorder”[MeSH] OR “mental disorders”[MeSH] OR “intellectual disability”[tiab] OR “mental disorders diagnosed in childhood”[MeSH] OR “depression”[tiab] OR “bipolar”[tiab] OR “school”[tiab] OR “developmental score”[tiab] OR “developmental scores”[tiab] OR "IQ"[tiab] OR “intellectual quotient”[tiab] OR “neural index”[tiab] OR “neural indices"[tiab] OR “motor development”[tiab]

**AND**

“child”[MeSH] OR “infant”[MeSH] OR “pregnancy”[MeSH] OR “pregnant women” [MeSH] OR “child”[tiab] OR “children”[tiab] OR “childhood”[tiab] OR “infant”[tiab] OR “infants”[tiab] OR “pregnant”[tiab] OR “pregnancy”[tiab] OR “prenatal”[tiab] OR “maternal”[tiab] OR “lactation”[MeSH] OR “lactation”[tiab] OR “breast feeding”[MeSH] OR “breast-feed”[tiab] OR baby[tiab] OR babies[tiab]

**AND**

“clinical trial” [MeSH] OR “randomized controlled trial” [MeSH] OR “meta-analysis” [MeSH] OR “cohort studies” [MeSH] OR “longitudinal studies” [MeSH] OR “random allocation” [MeSH] OR “clinical trial” [ptyp] OR “controlled clinical trial” [ptyp] or “randomized controlled trial” [ptyp] OR “meta-analysis” [ptyp] OR “clinical trial” [tiab] OR “randomized controlled trial” [tiab] OR “trial” [tiab] OR “meta-analysis” [tiab] OR “cohort” [tiab] OR “longitudinal” [tiab] OR “random” [tiab] OR prospective[tiab] OR “comparative study”[ptyp] OR “multicenter study”[ptyp] OR risk assessment[MeSH]

**Search strategy in other databases**

We adapted the PubMed search strategy for use in EMBASE, PsycInfo, and the Cochrane Library. Clinicaltrials.gov was searched on April 25, 2016 using the following search terms: “DHA” AND “development”

**Prospective cohorts and child supplementation (>24 months)**

We searched for all randomized controlled trials or prospective cohorts, though following full-text review, we limited our scope to trials only. Additionally, we did not impose an age limit on our search or title and abstract screen. At the full-text review stage, we identified and subsequently excluded 3 trials from 2 publications that provides supplements to school-aged children (> age 2 years) (62, 64).

**Author contact results**

Clarification of trial details or data only reported in figures were requested up to 3 times via e-mail from the authors of the following studies: (27, 29, 31, 33-36, 39, 43-45, 57, 69, 75, 76). Requested data were provided by: (33, 39, 43, 45). Data not provided were estimated from published figures using Plot Digitizer (http://plotdigitizer.sourceforge.net/). Bayley Scales of Infant Development results were not reported in any extractable way in Gibson et al. (44), and thus could not be included in the meta-analysis. Bayley Scales of Infant Development results at 6 months were not reported in any extractable way in Ben et al. (29), but were extracted directly from the Cochrane review by Simmer et al. (17). Review authors were provided raw data from Ben et al. (29) upon request, and the review reported sample size, mean, and SD for intervention and control groups.

**Supplemental Methods 2.**  Statistical methods

**Estimating mean and SD from suboptimal reported metrics.**

Median and corresponding measures of uncertainty (standard error, interquartile range, or 95% confidence intervals) were extracted when the primary metrics were not reported, and converted to mean and SD using a standardized approach described below.

|  |
| --- |
| 1. To estimate mean and SD when only median and interquartile range (IQR): Using methods proposed by Wan et al. (77), pages 10 and 16.
 |
| 1.1. To estimate mean (equation 14): |
| Macintosh HD:Users:mshulk01:Desktop:Screen Shot 2016-02-24 at 11.44.54 AM.png |
| 1.2. To estimate SD when sample size ≤50 (equation 15 and table 2): |
| Macintosh HD:Users:mshulk01:Desktop:Screen Shot 2016-02-24 at 11.45.39 AM.pngMacintosh HD:Users:mshulk01:Desktop:Screen Shot 2016-02-24 at 11.45.00 AM.png |
| 1.3. To estimate SD when sample size >50 (equation 17): |
| Macintosh HD:Users:mshulk01:Desktop:Screen Shot 2016-02-24 at 11.45.18 AM.png |

|  |
| --- |
| 2. To estimate SD when only standard error (SE) reported: Using methods proposed by the Cochrane handbook (21), section 7.7.3.2 |
| SD = SE \* √*n* |
| 1. To estimate SD when only p-value reported: Using methods proposed by the Cochrane handbook (21), section 7.7.3.3
 |
| SE=MD/t, where: t=t value, can be calculated by entering in the following formula to excel: =tinv(*P*-value,df)df=degrees of freedom, n-1MD=difference in means between intervention and control When levels of significance are reported rather than an exact p-value, we followed a conservative approach of taking the *P*-value at the upper limit (e.g. for *P*<0.05, use *P*=0.05).  |

**Converting cycles/degree to logMAR**

We identified numerous publications that reported visual acuity in metrics such as cycles/degree, logMAR, log arc s, microvolt, and millisecond. Upon consultation with experts in pediatric ophthalmology, we determined that only cycles/degree and logMAR could be combined together. It is increasingly common to express visual acuity from research and clinical work in logMAR, so we converted cycle/deg results to logMAR and SD logMAR using an equation reported in Qawasmi et al. (57).

$mean logMAR$ = $log\_{10 }(\frac{30}{mean cycle degree})$

$SD logMAR$= $\left(SD\_{of cycle/deg} in octaves\right)×0.3$

**Combining multiple BSID editions**

We used the BSID-III motor facet as the PDI estimate, and we used a weighted average of the BSID-III cognitive and language facets as the MDI estimate. Psychometric studies have indicated that scores differ between editions of BSID; specifically, that lower scores are observed when children are tested with BSID-II than with either BSID-I or BSID-III; and that this difference is nonlinear (78). To account for this, we planned to perform subgroup analysis on test edition, if there was sufficient power. However, only two trials that reported BSID-III met inclusion criteria; thus we performed sensitivity analysis excluding these two trials.

**Publications that did not report primary metrics**

|  |  |  |  |
| --- | --- | --- | --- |
| **Publication** | **Unit reported** | **Unit converted to** | **How was the conversion done?** |
| Smithers et al. 2011 | Cycles/degree | logMAR | See “converting cycles/degree to logMAR” section above |
| Innis et al. 2008 | Cycles/degree | logMAR | See “converting cycles/degree to logMAR” section above |
| Judge et al. 2007 | Cycles/degree | logMAR | See “converting cycles/degree to logMAR” section above |
| Hoffman et al. 2004 | Cycles/degree | logMAR | See “converting cycles/degree to logMAR” section above |
| Auestad et al. 2003 | Cycles/degree | logMAR | See “converting cycles/degree to logMAR” section above |
| Van Wezel-Meijler et al. 2002  | Cycles/degree | logMAR | See “converting cycles/degree to logMAR” section above |
| O’Connor et al. 2001 | Cycles/degree | logMAR | See “converting cycles/degree to logMAR” section above |
| Carlson et al. 1996 | Cycles/degree | logMAR | See “converting cycles/degree to logMAR” section above |
| Jensen et al. 2010 | Cycles/degree | logMAR | See “converting cycles/degree to logMAR” section above |
| Carlson et al. 1993 | Cycles/degree | logMAR | See “converting cycles/degree to logMAR” section above |
| Jensen et al. 2005 | Cycles/degree | logMAR | See “converting cycles/degree to logMAR” section above |
| Birch et al. 2005 | In figure only | Mean, SD | Plotdigitizer |
| Clandinin et al. 2005 | In figure only | Mean, SD | Plotdigitizer |
| Birch et al. 2002 | In figure only | Mean, SD | Plotdigitizer |
| Jorgensen et al. 1997 | In figure only | Mean, confidence intervals | Plotdigitizer |
| Uauy-Dagach et al. 1994 | In figure only | Mean | Plotdigitizer |
| Makrides et al. 2005 | In figure only | Mean, SD | Plotdigitizer |
| Carlson et al. 1993 | In figure only | Mean, SD | Plotdigitizer |
| Makrides et al. 2010 | Cognitive, language facets (BSID III) | MDI | Weighted average |
| Meldrum et al. 2012 | Cognitive, language facets (BSID III) | MDI | Weighted average |
| Makrides et al. 2010 | Motor facet (BSID III) | PDI | 1:1 ratio |
| Meldrum et al. 2012 | Motor facet (BSID III) | PDI | 1:1 ratio |
| Uauy-Dagach et al. 1994 | p-value | SD | See section 3 in table 2.1 |
| Colombo et al. 2013 | SE | SD | See section 2 in table 2.1 |
| Birch et al. 2010 | SE | SD | See section 2 in table 2.1 |
| Birch et al. 2007 | SE | SD | See section 2 in table 2.1 |
| Clandinin et al. 2005 | SE | SD | See section 2 in table 2.1 |
| Birch et al. 2000 | SE | SD | See section 2 in table 2.1 |
| Jorgensen et al. 1997 | Upper and lower confidence intervals | SD | See section 1 in table 2.1 |
| Colombo et al. 2013 | Received data from author contact (reported data was in SE, so we converted it to SD) |
| Birch et al. 2010 | Received data from author contact (reported data was in SE, so we converted it to SD) |
| Helland et al. 2008 | Received data from author contact |
| Fewtrell et al. 2004 | Received data from author contact |
| Ben et al. 2004 | Used data reported in Simmer et al. (18). This paper reported that they received the data through author contact.  |

|  |
| --- |
| **Supplemental Table 1.** Risk of bias assessment of each included trial 1 |
| Author  | Year | Population | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective Reporting | Overall quality score 2 |
| Meldrum [61] | 2015 | Maternal | 1 | 1 | 1 | 1 | -1 | 1 | 4 |
| Ramakrishnan [65] | 2015 | Maternal | 1 | 1 | 1 | 1 | 1 | 1 | 6 |
| Hurtado [49] | 2015 | Maternal | 1 | 0 | 1 | 1 | -1 | 1 | 3 |
| Campoy [35] | 2011 | Maternal | 1 | 0 | 1 | 1 | -1 | 1 | 3 |
| van Goor [70] | 2011 | Maternal | 0 | 0 | 1 | 1 | -1 | 1 | 2 |
| Makrides 3 [59] | 2010 | Maternal | 1 | 1 | 1 | 1 | 1 | 1 | 6 |
| Helland [45] | 2008 | Maternal | 1 | 0 | 1 | 1 | -1 | 1 | 3 |
| Innis [50] | 2008 | Maternal | 1 | 1 | 1 | 1 | -1 | 1 | 4 |
| Judge [54] | 2007 | Maternal | 1 | 0 | 1 | 1 | -1 | 1 | 3 |
| Tofail [68] | 2006 | Maternal | 0 | 0 | 1 | 1 | -1 | 1 | 2 |
| Jensen [52] | 2005 | Maternal | 1 | 1 | 1 | 1 | -1 | 1 | 4 |
| Lauritzen [55] | 2004 | Maternal | 1 | 0 | 1 | 1 | 1 | 1 | 5 |
| Gibson [44] | 1997 | Maternal | 0 | 0 | 1 | 1 | -1 | 1 | 2 |
| Isaacs 4 [51] | 2011 | Pre-term infant | 1 | 1 | 1 | 1 | -1 | 1 | 4 |
| Fang [42] | 2005 | Pre-term infant | 1 | 0 | 1 | 1 | -1 | 1 | 3 |
| Clandinin [38] | 2005 | Pre-term infant | 1 | 0 | 1 | 1 | -1 | 1 | 3 |
| van Wezel-Meijler [71] | 2002 | Pre-term infant | 1 | 1 | 1 | 1 | -1 | 1 | 4 |
| O'Connor [63] | 2001 | Pre-term infant | 1 | 0 | 0 | 0 | 1 | 1 | 3 |
| Uauy-Dagach [69] | 1994 | Pre-term infant | 0 | 0 | 0 | 0 | -1 | 1 | 0 |
| Carlson [36] | 1993 | Pre-term infant | 0 | 0 | 0 | 1 | -1 | 1 | 1 |
| Colombo [39] | 2013 | Term infant | 1 | 1 | 1 | 1 | -1 | 1 | 4 |
| Willatts [72] | 2013 | Term infant | 1 | 1 | 1 | 1 | -1 | 1 | 4 |
| Meldrum [60] | 2012 | Term infant | 1 | 1 | -1 | 1 | -1 | 1 | 2 |
| Drover [40] | 2011 | Term infant | 1 | 1 | 1 | 1 | -1 | 1 | 4 |
| Birch [32] | 2007 | Term infant | 1 | 1 | 1 | 1 | -1 | 1 | 4 |
| Agostoni [26] | 2006 | Term infant | 1 | 1 | 1 | 1 | -1 | 1 | 4 |
| Birch [31] | 2005 | Term infant | 1 | 1 | 1 | 1 | -1 | 1 | 4 |
| Hoffman [47] | 2004 | Term infant | 1 | 0 | 0 | 0 | -1 | 1 | 1 |
| Ben [29] | 2004 | Term infant | 0 | 0 | 0 | 0 | -1 | 1 | 0 |
| Auestad [28] | 2003 | Term infant | 0 | 1 | 1 | 1 | -1 | 1 | 3 |
| Hoffman [43] | 2003 | Term infant | 1 | 1 | 0 | 0 | -1 | 1 | 2 |
| Birch [34] | 2002 | Term infant | 1 | 1 | 0 | 1 | -1 | 1 | 3 |
| Auestad [27] | 2001 | Term infant | 1 | 0 | 1 | 1 | -1 | 1 | 3 |
| Makrides [58] | 2000 | Term infant | 1 | 1 | 1 | 1 | 1 | 1 | 6 |
| Lucas [56] | 1999 | Term infant | 1 | 1 | 1 | 1 | 1 | 1 | 6 |
| Jorgensen [48] | 1998 | Term infant | 0 | 0 | 1 | 0 | -1 | 1 | 1 |
| Carlson [37] | 1996 | Term infant | 0 | 0 | 1 | 1 | -1 | 1 | 2 |
| Makrides [57] | 1995 | Term infant | 0 | 0 | 1 | 1 | -1 | 1 | 2 |
| 1 For assessment of the effect of quality score in meta-regression, quality score was assessed per each outcome to account for differences in quality score for multiple publications of the same trial. Most publications of a single trial were given the same quality score (Drover et al. 2011 and Birch et al. 2010; Birch et al. 2007 and Birch et al. 2000; Jensen et al. 2005 and Jensen et al. 2010; Auestad et al. 2003 and Scott et al. 1998). Exceptions noted in footnotes below.2 Quality scores calculated using the Cochrane Risk of Bias Tool, with each of 6 criterion (excluding the 7th “other bias” criterion) received a score of low (+1), high (-1), or unclear (0) risk of bias. These values were summed to generate the reported overall quality score.3 Overall quality score for Smithers et al. 2011 (67) = 4. Despite double blinding, publication reports that 62% of intervention group correctly guessed assignment compared to 13% of control group. Therefore, this publication was rated as having a high risk of bias of knowledge of allocated intervention by participants and personnel during the study.4 Overall quality score for Fewtrell et al. 2004 (43) = 6. This analysis was performed on an intention-to-treat basis, which contributed to this publication being rated as having a low risk of bias of incomplete outcome assessment. |

|  |
| --- |
| **Supplemental Table 2.** Study characteristics of maternal n-3 supplementation trials |
| Author, year, trial | Country | Race | SES | Education | Maternal age, yr | Intervention period | Duration, wk | Compound given to both groups | Main intervention | Dose, mg/d | Control | Outcome | Latest age at outcome assessment, mo | Quality Score1 |
| DHA | EPA | AA | BSID | Visual | IQ |
| **Hurtado et al. 2015 (79)** | Spain | White2 | .m | .m | 30.2 | 28th wk until delivery + 4 mo lactation | 29.2 | dairy drink with vitamins and minerals3 | DHA + EPA | 320 | 72 | - | Control dairy drink | BSID | 12 | - | - | 3 |
| **Meldrum 2015 (61)** | Australia | White2 | .m | high | 31.8 | 20th wk until delivery | 20 | Vitamin E | DHA + EPA | 2200 | 1100 | - | Olive oil | WISC | - | - | 144 | 4 |
| **Dunstan 2008 (41)** | Griffiths 4 | - |
| **Ramakrishnan 2015 (65)** | Mexico | Hispanic2 | med-low | average | 26.4 | 18-20th wk until delivery | 20 | - | DHA | 400 | 0 | - | Olive oil | BSID | 18 | - | - | 6 |
| **Campoy 2011, NUHEAL (35)** | Germany, Spain, Hungary | >99% white | .m | average | 31.0 | 20th wk until delivery5 | 20 | milk-based supplement with vitamins and minerals6 | DHA + EPA ± 400 μg 5-methyltetrahyro-folate 7 | 500 | 150 | - | Control milk-based supplement | K-ABC | - | - | 81 | 3 |
| **Smithers 2011, DOMInO (67)** | Australia | White2 | .m | average | 29.1 | 19th wk (median) until delivery | 21 | - | DHA + EPA | 800 | 100 | - | Vegetable oil | VEP | - | 4 | - | 4 8 |
| **Makrides 2010, DOMInO (59)** | 28.9 | Vegetable oil | BSID-III | 18 | - | - | 6 |
| **Van Goor 2011 (70)** | Netherlands | White2 | .m | average | 32.7 | 16.5th wk until delivery + 3 mo lactation | 36 | - | 1) DHA + EPA + higher AA | 220 | 36 | 220 | Soybean oil | BSID | 18 | - | - | 2 |
| 2) DHA + EPA + lower AA | 15 |
| **Jensen 2010 (80)** | USA | 79% white | .m | high | 31.6 | Within 5 d of delivery, 4 mo lactation | 17.2 | - | DHA | 200 | 0 | - | Corn + soy oil | VEP | - | 64 | - | 4 |
| **Jensen 2005 (52)** | 77% white | 31.5 | BSID | 30 | - | - | 4 |
| **Helland 2008 (45)** | Norway | White2 | .m | high | 29.2 | 18th wk until delivery + 3 mo lactation | 35 | Vitamins A, D, E | DHA + EPA | 1183 | 803 | 27.5 | Corn oil 9 | K-ABC | - | - | 84 | 3 |
| **Innis 2008 (50)** | Canada | 73% white | med-high | high | 33.2 | 16th wk until delivery | 24 | - | DHA | 400 | 0 | - | Vegetable oil | TAC | - | 2 | - | 4 |
| **Judge 2007 (54)** | USA | 93% black | low | average | 24.3 | 24th wk until delivery | 16 | cereal-based bar | DHA + EPA | 214 10 | 26.80 11 | - | Cereal bar with corn oil | TAC | - | 6 | - | 3 |
| **Tofail 2006 (68)** | Bangladesh | Asian2 | low | low | 22.7 | 25th wk until delivery | 15 | - | DHA + EPA | 1200 | 1800 | - | Vegetable oil | BSID | 10 | - | - | 2 |
| **Lauritzen 2004 (55)** | Denmark | White2 | .m | high | 29.9 | within 9 d of delivery, 4 mo lactation | 17.2 | - | DHA + EPA | 790 | 620 | 1.7% FA | Olive oil | VEP | - | 4 | - | 5 |
| **Gibson 1997 (44)** | Australia | White2 | med | average | 30 | Within 5 d of delivery, 12 wk lactation | 12 | - | 1) DHA dose 1 | 200 | 0 | - | Oil, not further specified | VEP | - | 3.7 | - | 2 |
| 2) DHA dose 2 | 400 |
| 3) DHA dose 3 | 900 |
| 4) DHA dose 4 | 1300 |
| *Abbreviations: AA, arachidonic acid; BSID, Bayley Scales of Infant Development; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acids; IQ, Intelligence Quotient; K-ABC, Kaufman Assessment Battery for Children; .m, missing (not reported in publication); TAC, Teller Acuity Cards; VEP, Visual Evoked Potentials; WISC, Wechsler Intelligence Scale for Children.*1 Quality scores calculated using the Cochrane Risk of Bias Tool (21), with each of 6 criterion (excluding the 7th “other bias” criterion) received a score of low (+1), high (-1), or unclear (0) risk of bias. These values were summed to generate the reported overall quality score. 2 Race not reported, assume based on predominant race in trial country, if country is racially homogenous. 3 Vitamins and minerals included 80μg/100mL folic acid, 2.2 mg/100mL iron, 23 μg/100mL iodine, 0.4 μg/100mL vitamin B-12. Additionally, both groups received a recommended diet developed by a nutritionist, which highlighted the recommendation for weekly fish consumption.4 Other infant development outcomes, such as Griffiths Mental Development Scales, not included in meta-analysis. 5 After delivery, intervention children who were not breastfed received DHA/AA-supplemented formula.6 300 mg Ca, 240 mg P, 93 mg Mg, 3 mg Zn, 66 μg I; vitamins: 330 μg vitamin A, 1.5 μg vitamin D, 3 mg vitamin E, 0.36 mg thiamine, 1.5 mg riboflavin, 4.5 mg vitamin B-3, 1.9 mg vitamin B-6, 3.5 μg vitamin B-12, 270 mg vitamin C.7 Since this trial employed a 2x2 factorial design, we pooled the two DHA-containing groups (DHA + EPA only and DHA +EPA + 5-methyltetrahyro-folate) using a weighted average calculation. 8 Two trials (one maternal, one pre-term infant) with two publications each were assigned different quality scores between publications. Despite double blinding, study reports that 62% of intervention group correctly guessed assignment compared to 13% of control group. Therefore, this publication was rated as having a high risk of bias of knowledge of allocated intervention by participants and personnel during the study.9 Corn oil contained a small amount of DHA (8.3 mg/day)10 DHA dose from the following statement in methods section "women consumed 3, 5, or 7 bars weekly… the consumption of an average of 5 bars per week provided 214 mg DHA/day"11 EPA dose calculated from the 1:8 EPA:DHA ratio reported in the methods section. |

|  |  |
| --- | --- |
| **Supplemental Table 3.** Study characteristics of pre-term infant n-3 supplementation trials |  |
| Author, year | Country | Race  | SES | Maternal education | GA, wk1 | Duration, wk 2 | Main intervention | Dose, %FA | Outcome | Latest age at outcome assessment, mo | Quality Score 3 |
| DHA | EPA | AA | BSID | Visual  | IQ |
| **Isaacs 2011 (51)** | UK | White 4 | 23% high SES  | low | 30.8 | 47.9 5 | DHA + EPA + AA  | 0.5 | 0.1 | 0.04 | WASI | - | - | 130 | 4 |
| **Fewtrell 2004 (43)** | 31.2 | 47.5 | BSID, KPS 6 | 18 | - | - | 6 7 |
| **Fang 2005 (42)** | Taiwan | Asian 4 | .m | .m | 35.6 | 30.2 | DHA + AA | 0.05 | 0 | 0.1 | BSID, VEP | 12 | 6 | - | 3 |
| **Clandinin 2005 (75)** | Australia | White 4 | .m | .m | 29.4 | 60.9 | 1) DHA + AA | 0.32 8 | 0 | 0.64 | BSID | 18 | - | - | 3 |
| 2) DHA + EPA + AA | 0.1 |
| **Van Wezel-Meijler 2002 (71)** | Netherlands | White 4 | .m | .m | 30.4 | 35.4 | DHA + AA | 0.34 | 0 | 0.7 | BSID, TAC | 24 | 24 | - | 4 |
| **O’Connor 2001 (63)** | USA, UK, Chile | 82% white | .m | .m | 29.8 | 61.9 | 1) DHA + EPA + AA | 0.188 | 0.01 | 0.43 | BSID, VEP | 12 | 6 | - | 3 |
| 2) DHA + AA | 0.17 | 0 | 0.41 |
| **Uauy Dagach 1994 (69)** | USA, Chile | .m | .m | .m | 30 | 27 | DHA + EPA + AA | 0.35 | 0.65 | 0.1 | VEP | - | 4 | - | 0 |
| **Carlson 1993 (36)** | USA | 88% black | low | .m | 29 | 53.6 | DHA + EPA | 0.3 | 0.2 | 0 | TAC | - | 12 | - | 1 |
| *Abbreviations: AA, arachidonic acid; BSID, Bayley Scales of Infant Development; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acids; IQ, Intelligence Quotient; KPS,*  *Knobloch, Passamanick, and Sherrads Developmental Screening Index; .m, missing; TAC, Teller Acuity Cards; VEP, Visual Evoked Potentials; WASI, Wechsler Abbreviated Scale of Intelligence.* 1 Gestational age at birth2 Supplementation duration for pre-term infants calculated taking into account duration until term gestational age. Supplementation start varied substantially (e.g. within 1-60 days of birth in one trial), but since mean start was within two weeks of birth for all trials except one, we calculated a conservative supplementation duration using gestational age at birth as follows when trials only reported supplementation end in months post-term: (40 weeks – mean gestational age at birth) + (supplementation end in months post-term \* 4.3 weeks/month). In Carlson et al. 1993, where mean supplementation start was 25 days, we added 25 days to the calculation above. 3 Quality scores calculated using the Cochrane Risk of Bias Tool (21), with each of 6 criterion (excluding the 7th “other bias” criterion) received a score of low (+1), high (-1), or unclear (0) risk of bias. These values were summed to generate the reported overall quality score.4 Race not reported, assume based on predominant race in trial country, if country is racially homogenous.5 Estimated duration is slightly different between Isaacs et al. 2011 and Fewtrell et al. 2004 because mean gestational age at birth was different. 6 Other infant development outcomes, such as KPS, not included in meta-analysis.7 Two trials (one maternal, one pre-term infant) with two publications each were assigned different quality scores between publications. The analysis in Fewtrell et al. 2004 was performed on an intention-to-treat basis, which contributed to this publication being rated as having a low risk of bias of incomplete outcome assessment.8 When pre-term infant supplementation trials included formulas of varying fatty acid compositions before and after infants reached term corrected age (i.e. different pre- and post-term formulas), we calculated the weighted average dose of supplementation based on the reported doses and average duration between baseline and term corrected age (40 weeks minus average gestational age) and between term corrected age and intervention end. This calculated weighted average dose approximated the term formula composition since pre-term supplementation trials were at least 6 months in length.  |

|  |
| --- |
| **Supplemental Table 4.** Study characteristics of term infant n-3 supplementation trials |
| Author, year, trial | Country | Race | SES | Maternal education | Baseline age | Duration wk 1 | Main intervention | Dose, % FA2 | Outcome  | Latest age at outcome assessment, mo | Quality Score 3 |
| DHA | EPA | AA | BSID | Visual | IQ |
| **Colombo 2013, DIAMOND *phase II Kansas City* (39)** | USA | 61% black | low | average | at birth | 51.6 | 1) 1:2 DHA:AA | 0.32 | 0 | 0.64 | BSID | 18 | - | - | 4 |
| 2) 1:1 DHA:AA | 0.64 |
| 3) 2:1 DHA:AA | 0.96 |
| **Willatts 2013 (72)** | UK, Belgium, Italy  | White4 | .m | average | within 3 d of birth | 17.2 | DHA + AA | 0.21 | 0 | 0.35 | WPPSI | - | - | 70 | 4 |
| **Meldrum 2012, IFOS (81)** | Australia | 91% white | high | high | at birth | 25.8 | DHA + EPA | 276 mg 5 | 100 mg | 0 | BSID-III | 18 | - | - | 2 |
| **Drover 2011 DIAMOND *phase II Dallas* (40)** | USA | 69% white | .m | high | within 9 d of birth | 51.6 | 1) 1:2 DHA:AA | 0.32 | 0 | 0.64 | BSID | 18 | - | - | 4 |
| **Birch 2010 DIAMOND *phase II Dallas* (33)** | 58% white, 36% black | average | VEP | - | 12 | - | 6 |
| **Drover 2011 (40)** | 69% white | high | 2) 1:1 DHA:AA | 0.64 | 0 | 0.64 | BSID | 18 | - | - | 4 |
| **Birch 2010 (33)**  | 58% white, 36% black | average | VEP | - | 12 | - | 6 |
| **Drover 2011 (40)** | 69% white | high | 3) 2:1 DHA:AA | 0.96 | 0 | 0.64 | BSID | 18 | - | - | 4 |
| **Birch 2010 (33)**  | 58% white, 36% black | average | VEP | - | 12 | - | 6 |
| **Agostoni 2006 (26)** | Western Europe | White4 | .m | .m | Mean 19 d after PKU diagnosis | 49.4 | DHA + AA | 0.3 | 0 | 0.7 | BSID | 12 | - | -  | 4 |
| **Birch 2007 (82)** | USA | 81% white | .m | high | within 4 d of birth; mean 2.1 d | 17 | 1) DHA | 0.35 | 0 | 0 | HOTV, WPPSI | - | 48 | 48 | 4 |
| **Birch 2000 (30)** | 75% white | BSID | 18 | - | **-** |
| **Birch 2007 (82)** | 81% white | 2) DHA + AA | 0.36 | 0 | 0.72 | HOTV, WPPSI | - | 48 | 48 |
| **Birch 2000 (30)** | 75% white | BSID | 18 | - | **-** |
| **Birch 2005 (31)** | USA | 79% white | .m | high | within 5 d of birth; mean 3.6 d | 52 | DHA + AA | 0.36 | 0 | 0.72 | VEP | - | 12 |  - | 4 |
| **Ben 2004 (29)** | China | Asian4 | .m | .m | within 7 d of birth | 25.8 | DHA + AA | 6.9 mg/L6 | 0 | 6.9 mg/L | BSID | 6 | - |  - | 0 |
| **Hoffman 2004 (47)** | USA | .m | .m | .m | after 6 mo breastfeeding | 25.8 | DHA + AA + EPA | 130mg 7 | 4.5mg | 88mg | VEP | - | 12 |  - | 1 |
| **Auestad 2003 (28)** | USA | 84% white | .m | high | 2 d (median) after birth | 51.6 | 1) DHA + EPA | 0.23 | 0.07 | 0 | Stanford-Binet, TAC | - | 39 | 39 | 3 |
| **Scott 1998 (66)** | BSID | 12 | - | -  |
| **Auestad 2003 (28)** | 2) DHA + AA | 0.12 | 0 | 0.43 | Stanford-Binet, TAC | - | 39 | 39 |
| **Scott 1998 (66)** | BSID | 12 | - | -  |
| **Hoffman 2003 (83)** | USA | 93% white | .m | .m | after 4-6 mo breastfeeding | 30.1 | DHA + AA | 0.36 | 0 | 0.72 | VEP | - | 12 |  - | 2 |
|  **Birch 2002 (34)** | USA | 77% white | .m | high | after 6 wk breastfeeding | 46 | DHA + AA | 0.36 | 0 | 0.72 | VEP | - | 12 | - | 3 |
| **Auestad 2001 (27)** | USA | 85% white | .m | high | within 9 d of birth | 51.6 | 1) DHA + AA | 0.14 | 0 | 0.45 | BSID, TAC | 12 | 12 | **-** | 3 |
| 2) DHA + AA + EPA | 0.13 | ≤0.04 | 0.46 |
| **Makrides 2000 (58)** | Australia | White4 | low | low | within 7 d of birth | 51.6 | 1) DHA + EPA | 0.35 | 0.1 | 0 | BSID, VEP | 24 | 7.9 | - | 6 |
| 2) DHA + AA | 0.34 | 0 | 0.34 |
| **Agostoni 1997 (25)** | Italy | White4 | .m | .m | within 3 d of birth | 21.5 | DHA + EPA + AA | 0.3 | 0.05 | 0.44 | Brunet-Lezine 8 | - | - | -  | 4 |
| **Lucas 1999 (56)** | UK | White4 | med | low | within 7 d of birth | 25.8 | DHA + AA + EPA | 0.32 | 0.01 | 0.3 | BSID, KPS 8 | 18 | - | -  | 6 |
| **Jorgensen 1998 (76)** | Denmark | White4 | .m | .m | 25 d to 4 mo old | 13.6 | DHA + EPA + AA9  | 0.32 | 0.38 | 0.06 | VEP | - | 4 |  - | 1 |
| **Carlson 1996 (37)** | USA | 90% black | low | .m | .m | 51.6 | DHA + AA | 0.1 | 0 | 0.43 | TAC | - | 12 |  - | 2 |
| **Makrides 1995 (57)** | Australia | White4 | low | low | within 4-6 d of birth | 30 | DHA + EPA + AA 10 | 0.36 | 0.58 | 0.01 | VEP | - | 7 |  - | 2 |
| *Abbreviations: AA, arachidonic acid; BSID, Bayley Scales of Infant Development; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FA, fatty acids; IQ, Intelligence Quotient; KPS,*  *Knobloch, Passamanick, and Sherrads Developmental Screening Index; .m, missing (not reported in publication); TAC, Teller Acuity Cards; VEP, Visual Evoked Potentials; WPPSI, Wechsler Preschool and Primary Scale of Intelligence.* |
| 1 There was a range in supplementation start dates in within trials. Therefore, for trials starting supplementation within first 10 days after birth, we calculated a conservative supplementation duration using the full time period until supplementation end. 2 Dose reported in % FA of infant formula, unless otherwise noted. 3 Quality scores calculated using the Cochrane Risk of Bias Tool (21), with each of 6 criterion (excluding the 7th “other bias” criterion) received a score of low (+1), high (-1), or unclear (0) risk of bias. These values were summed to generate the reported overall quality score.4 Race not reported, assume based on predominant race in trial country, if country is racially homogenous.5 Infants in intervention group received a fish oil capsule; control infants received an image and scent-matched olive oil capsule. 6 Intervention was infant formula, but dose was only reported in mg/L and could not be converted to %FA. 7 Infants in intervention group received jarred baby food fortified with DHA-enriched egg yolk; control infants received the same baby food without the enriched egg yolk. 8 Other infant development outcomes reporting overall developmental quotient, such as Brunet-Lezine and KPS, not included in meta-analysis.9 Trial included two intervention arms (+/- 0.5%FA of gamma-linolenic acid from borage oil), which were pooled in the outcome reported by the publication. 10 Intervention included fish oil and evening primrose oil (which supplied gamma-linolenic acid) in a 1:1 ratio.  |

|  |
| --- |
| **Supplemental Table 5. Subgroup meta-analyses of maternal and infant n-3 supplementation on cognitive and visual development.** |
|   | BSID - Mental Developmental Index |   | BSID - Psychomotor Developmental Index |   | Visual Acuity |   | Intelligence Quotient |
|   | *n* | MD (95% CI) | *I2* | *Phet1* |  | *n* | MD (95% CI) | *I2* | *Phet1* |  | *n* | MD (95% CI) | *I2* | *Phet1* |  | *n* | MD (95% CI) | *I2* | *Phet1* |
| **Main analysis**  | 32 | 0.906(0.005, 1.807) | 27.0% |  |  | 32 | 1.064(0.099, 2.030) | 42.3% |  |  | 33 | -0.063(-0.084, -0.041) | 81.6% |  |  | 9 | 0.198(-1.565, 1.960) | 0% |  |
| **Period of intervention** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Maternal | 7 | -0.360(-1.299, 0.578) | 0% |  |  | 7 | 1.015(-0.518, 2.548) | 48.5% |  |  | 9 | -0.016(-0.036, 0.003) | 0% |  |  | 3 | 0.352(-2.110, 2.814) | 0% |  |
| Pre-term infant | 7 | 3.325(0.718, 5.932) | 45.0% | **0.018** |  | 7 | 2.294(-1.080, 5.668) | 58.8% | 0.779 |  | 6 | -0.078(-0.144, -0.011) | 67.1% | 0.115 |  | 5 | 2.400(-2.456, 7.256) | 38.3% | 0.508 |
| Term infant | 18 | 0.986(-0.258, 2.229) | 7.6% | 0.157 |  | 18 | 0.840(-0.484, 2.165) | 34.8% | 0.775 |  | 18 | -0.083(-0.113, -0.052 | 87.8% | **0.022** |  | 1 | -0.368(-4.239, 3.503) | - | 0.583 |
| **World region** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Western | 26 | 1.441(0.235, 2.648) | 25.4% |  |  | 26 | 1.062(-0.124, 2.247) | 42.3% |  |  | 29 | -0.057(-0.079, -0.035) | 82.7% |  |  | 9 | 0.198(-1.565, 1.960) | 0% | - |
| Other | 6 | 0.635(-1.042, 2.313) | 54.4% | 0.459 |  | 6 | 0.980(-0.807, 2.766) | 46.9% | 0.889 |  | 4 | -0.139(-0.194, -0.084) | 0.0% | 0.105 |  | - | - | - | - |
| **Maternal education** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| High | 11 | 1.947(0.131, 3.764) | 35.6% |  |  | 11 | 1.493(-0.452, 3.437) | 59.6% |  |  | 11 | -0.041(-0.063, -0.019) | 72.7% |  |  | 6 | 0.492(-2.052, 3.037) | 9.6% |  |
| Other/missing | 21 | 0.393(-0.565, 1.352) | 17.0% | 0.200 |  | 21 | 0.577(-0.391, 1.544) | 19.1% | 0.119 |  | 22 | -0.075(-0.107, -0.042) | 73.8% | 0.207 |  | 3 | -0.154(-2.975, 2.666) | 9.7% | 0.757 |
| **Race/ethnicity** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| White | 25 | 1.144(0.070, 2.218) | 21.5% |  |  | 25 | 1.179(0.036, 2.322) | 42.3% |  |  | 27 | -0.061(-0.084, -0.038) | 83.4% |  |  | 9 | 0.198(-1.565, 1.960) | 0% | - |
| Other/missing | 7 | 0.401(-1.357, 2.158) | 42.4% | 0.424 |  | 7 | 0.699(-1.297, 2.695) | 43.3% | 0.643 |  | 6 | -0.077(-0.171, 0.017) | 68.5% | 0.665 |  | - | - | - | - |
| **Duration** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ≤ mean 2 | 11 | 1.055(-0.361, 2.470) | 49.5% |  |  | 11 | 1.381(0.127, 2.634) | 53.3% |  |  | 17 | -0.042(-0.061, -0.024) | 58.5% |  |  | 5 | 0.648(-2.306, 3.602) | 19.3% |  |
| > mean  | 21 | 0.869(-0.334, 2.072) | 9.8% | 0.937 |  | 21 | 0.609(-0.927, 2.144) | 38.0% | 0.51 |  | 16 | -0.077(-0.115, -0.039) | 79.2% | 0.204 |  | 4 | -0.009(-2.432, 2.414) | 0% | 0.824 |
| **DHA dose** 3 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ≤ mean 2 | 20 | 0.679(-0.491, 1.850) | 26.6% |  |  | 20 | 0.851(-0.554, 2.256) | 50.5% |  |  | 23 | -0.061(-0.085, -0.038) | 76.3% |  |  | 6 | -0.462(-3.317, 2.394) | 23.8% |  |
| > mean | 10 | 1.830(-0.001, 3.661) | 37.5% | 0.383 |  | 10 | 1.223(-0.463, 2.909) | 35.0% | 0.751 |  | 9 | -0.051(-0.104, 0.002) | 86.0% | 0.810 |  | 3 | 1.115(-1.469, 3.699) | 0% | 0.373 |
| **EPA dose** 3 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| ≤ mean 2 | 27 | 1.120(0.026, 2.215) | 35.3% |  |  | 27 | 1.044(-0.080, 2.169) | 46.4% |  |  | 25 | -0.068(-0.092, -0.044) | 83.1% |  |  | 6 | 0.604(-1.984, 3.192) | 17.6% |  |
| > mean | 3 | 0.946(-0.882, 2.773) | 0% | 0.935 |  | 3 | 0.486(-4.041, 5.012) | 48.5% | 0.802 |  | 7 | -0.016(-0.061, 0.028) | 43.5% | 0.182 |  | 3 | -0.238(-2.996, 2.520) | 0% | 0.713 |
| **DHA:AA ratio** 4 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Continuous | 32 | 0.203(-0.575, 0.981) | 27.8% | 0.598 |  | 32 | -0.313(-1.312, 0.692) | 44.1% | 0.529 |  | 32 | -0.016 (-0.040, 0.008) | 82.2% | 0.185 |  | 9 | -0.490(-2.572, 1.592) | 7.0% | 0.595 |
| **Age at assessment** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Continuous, mo | 32 | 0.121(-0.0871, 0.330)- | 28.6% | 0.243 |  | 32 | 0.202(-0.0521, 0.455) | 41.7% | 0.115 |  | 33 | 0.001 (-0.0005, 0.003) | 76.1% | 0.185 |  | 9 | 0.026 (-0.041, 0.093) | 0% | 0.383 |
| ≤ median 2 | 11 | 0.378(-0.812, 1.568) | 8.5% |  |  | 11 | -0.231(-2.318, 1.857) | 49.2% |  |  | 16 | -0.041(-0.074, -0.009) | 47.1% |  |  | 4 | 0.739(-4.284, 5.763) | 45.3% |  |
| > median 2 | 21 | 1.517(0.213, 2.821) | 36.5% | 0.309 |  | 21 | 1.516(0.439, 2.594) | 39.0% | 0.174 |  | 17 | -0.075(-0.103, -0.047) | 88.8% | 0.251 |  | 5 | 0.179(-1.832, 2.191) | 0% | 0.973 |
| **Quality score** 5 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Continuous | 32 | -0.082(-0.657, 0.492) | 26.8% | 0.772 |  | 32 | -0.375 (-0.854, 0.104) | 39.4% | 0.120 |  | 33 | 0.007 (-0.015, 0.029) | 81.8% | 0.513 |  | 9 | 1.872 (-2.431, 6.176) | 0% | 0.338 |
| <3 | 15 | 0.672(-0.665, 2.009) | 33.7% |  |  | 15 | 1.079(-0.563, 2.721) | 48.1% |  |  | 20 | -0.059(-0.096, -0.022) | 64.2% |  |  | 4 | -0.595(-2.917, 1.726) | 0% |  |
| 4+ | 17 | 1.164(-0.122, 2.450) | 24.6% | 0.569 |  | 17 | 1.030(-0.174, 2.234) | 38.1% | 0.958 |  | 13 | -0.066(-0.095, -0.036) | 89.5% | 0.901 |  | 5 | 1.474(-1.674, 4.622) | 22.3% | 0.338 |
|  |
| *Abbreviations: AA, arachidonic acid; BSID, Bayley Scales of Infant Development; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MD, mean difference*1 Subgroup analyses were performed using stratified random-effects meta-analysis. P value for heterogeneity between subgroups based on random-effects meta-regression.2 In order to group maternal, pre-term, and term infant trials for subgroup analyses, we classified each trial as above or at/below mean or median of all intervention arms in that population. All mean/median values also reported in Table 1. Mean duration of supplementation (in weeks), by supplementation population: maternal=21.8; Pre-term infant=45.3; Term infant=37.2. Median age at outcome assessment (in months), by supplementation population and outcome: BSID MDI and PDI, maternal, pre-term infant and term infant=18; Visual acuity, maternal=4, pre-term infant=6, term infant=12; Intelligence quotient, maternal=84, pre-term infant=130, term infant=48. 3 Excluding three infant trials (29, 47, 81) that did not report DHA and EPA units in % fatty acids.4 Excluding one trial for visual acuity (55) that did not report DHA and AA in the same unit.5 Cumulative score (out of -6 to +6) on Cochrane Risk of Bias tool. |

**Supplemental Figure 1.** **PRISMA flow diagram of search strategy and identified studies.**

## Identification

**7043** records identified through PubMed (*n*=3069), EMBASE (*n*=1664), PsychInfo (*n*=322), Cochrane (*n*=1881), and ClinicalTrials.gov (*n*=107)

 **6286** records, after de-duplication, screened by title and abstract

## Screening

## Eligibility

## Included

**5617** records excluded

**669** full-text articles assessed for eligibility

**167** additional records identified through hand-searching of final included articles and related review articles, after de-duplication

**625** records excluded

**219** references/reviews

**115** design

**100** outcome

**75** duplicates

**48** population

**44** duration <3 mo

**24** exposure

**44** publications on **38** unique supplementation trials with standardized cognitive and visual outcomes (**53** intervention arms)

**Supplemental Figure 2**. Funnel plots

|  |
| --- |
| eFigure1.pdfFunnel plots graph variance (SE) versus effect size (MD), to assess asymmetry. **A)** Bayley Scales of Infant Development (BSID)- Mental Developmental Index (MDI) (*n*=32 intervention arms); Egger’s Test P=0.005; Duval and Tweedie’s Filled meta-analysis with random-effects (*n=*39 intervention arms) MD (95% CI): 0.17 (-0.90, 1.23). **B**) BSID-Psychomotor Developmental Index (PDI) (*n=*32 intervention arms); Egger’s Test P=0.393. **C)** Intelligence Quotient (*n=*9 intervention arms); Egger’s Test P=0.530. **D)** Visual acuity (*n=*33 intervention arms); Egger’s Test P=0.380.  |

**Supplemental 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. Annals of Nutrition and Metabolism 2009;55(1-3):76-96. doi: 10.1159/000228997.

2. Cheatham C. Omega-3 fatty acids and the development of cognitive abilities: a review of DHA supplementation studies. CAB Reviews: Perspectives in Agriculture, Veterinary Science, Nutrition and Natural Resources 2008;3(001). doi: 10.1079/pavsnnr20083001.

3. Nyaradi A, Li J, Hickling S, Foster J, Oddy WH. The role of nutrition in children's neurocognitive development, from pregnancy through childhood. Frontiers in Human Neuroscience 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(1-3):97-122. doi: 10.1159/000228998.

5. 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(2):281-95.

6. Innis SM. Omega-3 Fatty acids and neural development to 2 years of age: do we know enough for dietary recommendations? Journal of pediatric gastroenterology and nutrition 2009;48 Suppl 1:S16-24. doi: 10.1097/MPG.0b013e31819773cf.

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. doi: 10.1136/bmj.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(9561):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(10):1171-81. doi: 10.1093/aje/kwn034.

10. Farquharson J, Cockburn F, Patrick WA, Jamieson EC, Logan RW. Infant cerebral cortex phospholipid fatty-acid composition and diet. Lancet 1992;340(8823):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(2):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(3):531-44. doi: 10.3945/ajcn.112.045781.

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(6):1422-36. doi: 10.3945/ajcn.114.095315.

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(6):1141-9. doi: 10.1542/peds.2011-2127.

15. Qawasmi A, Landeros-Weisenberger A, Bloch MH. Meta-analysis of LCPUFA supplementation of infant formula and visual acuity. Pediatrics 2013;131(1):e262-72. doi: 10.1542/peds.2012-0517.

16. Schulzke SM, Patole SK, Simmer K. Long-chain polyunsaturated fatty acid supplementation in preterm infants. Cochrane Database Syst Rev 2011(2):Cd000375. doi: 10.1002/14651858.CD000375.pub4.

17. Simmer K, Patole SK, Rao SC. Long-chain polyunsaturated fatty acid supplementation in infants born at term. Cochrane Database Syst Rev 2011(12):Cd000376. doi: 10.1002/14651858.CD000376.pub3.

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(4):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. doi: 10.1002/14651858.CD007901.pub3.

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. doi: 10.1136/bmj.b2535.

21. Higgins JPT, Green S, (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011:Available from www.cochrane-handbook.org.

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):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(7109):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(2):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(5):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(3):207-12. doi: 10.1017/s0012162206000442.

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(2):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(8):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(3):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(4):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(5):279-84. doi: 10.1016/j.earlhumdev.2006.11.003.

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(4):848-59. doi: 10.3945/ajcn.2009.28557.

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(3):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):1880s-8s. doi: 10.3945/ajcn.110.001107.

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(1):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. Pediatric research 1996;39(5):882-8. doi: 10.1203/00006450-199605000-00024.

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(4):461-8. doi: 10.1016/j.jpeds.2004.11.030.

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(2):403-12. doi: 10.3945/ajcn.112.040766.

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 human development 2011;87(3):223-30. doi: 10.1016/j.earlhumdev.2010.12.047.

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(1):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 medical journal 2005;28(10):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. The Journal of pediatrics 2004;144(4):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(9):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(2):e472-9. doi: 10.1542/peds.2007-2762.

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(6):669-77. doi: 10.1067/mpd.2003.213.

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(9):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(4):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(4):472-80. doi: 10.1097/MPG.0000000000000864.

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(3):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(4):e890-8. doi: 10.1542/peds.2010-3153.

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(1):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(6):900-5. doi: 10.1016/j.jpeds.2010.06.006.

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(2):117-22. doi: 10.1007/s11745-006-3007-3.

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(3):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(9194):1948-54. doi: 10.1016/s0140-6736(99)02314-4.

57. Makrides M, Neumann M, Simmer K, Pater J, Gibson R. Are long-chain polyunsaturated fatty acids essential nutrients in infancy? Lancet 1995;345(8963):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(15):1675-83. doi: 10.1001/jama.2010.1507.

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(8):1443-54. doi: 10.1017/S0007114511006878.

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(3):2061-7. doi: 10.3390/nu7032061.

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. accessed Date Accessed)|.

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(2):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. accessed Date Accessed)|.

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(8):e0120065. doi: 10.1371/journal.pone.0120065.

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(5):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(6):1293-9. doi: 10.3945/ajcn.110.009647.

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(1):48-56.

69. Uauy-Dagach R, Mena P, Hoffman DR. Essential fatty acid metabolism and requirements for LBW infants. Acta paediatrica (Oslo, Norway : 1992) Supplement 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(5-6):139-46. doi: 10.1016/j.plefa.2011.01.002.

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(9):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(2):536S-42S. doi: 10.3945/ajcn.112.038612.

73. Wiesel TN. Postnatal development of the visual cortex and the influence of environment. Nature 1982;299(5884):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(1):e83764. doi: 10.1371/journal.pone.0083764.

75. 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. The Journal of pediatrics 2005;146(4):461-8. doi: 10.1016/j.jpeds.2004.11.030.

76. 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. Journal of pediatric gastroenterology and nutrition 1998;26(4):412-21.

77. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC medical research methodology 2014;14:135. doi: 10.1186/1471-2288-14-135.

78. Moore T, Johnson S, Haider S, Hennessy E, Marlow N. Relationship between test scores using the second and third editions of the Bayley Scales in extremely preterm children. J Pediatr 2012;160(4):553-8. doi: 10.1016/j.jpeds.2011.09.047.

79. 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. Journal of pediatric gastroenterology and nutrition 2015;61(4):472-80. doi: 10.1097/MPG.0000000000000864.

80. 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. The Journal of pediatrics 2010;157(6):900-5. doi: 10.1016/j.jpeds.2010.06.006.

81. 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(8):1443-54. doi: 10.1017/s0007114511006878.

82. 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 human development 2007;83(5):279-84. doi: 10.1016/j.earlhumdev.2006.11.003.

83. 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. The Journal of pediatrics 2003;142(6):669-77. doi: 10.1067/mpd.2003.213.