

Review Article**Maternal Docosahexaenoic Acid Supplementation and Infant Neurodevelopmental Outcomes at Twelve Months: A Randomized, Placebo-Controlled Trial****Schuster U^{1*}, Pichler J² and Hudakova M³**¹Department of Obstetrics and Gynaecology, Charite University Medicine Berlin, Berlin, Germany²Department of Paediatrics, Medical University of Vienna, Vienna, Austria³Department of Clinical Nutrition, Comenius University, Bratislava, Slovakia

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Abstract

Background: Docosahexaenoic acid (DHA) accumulates rapidly in the fetal and infant brain and retina, and maternal intake during pregnancy and lactation is often below recommended levels. **Objective:** To synthesise published evidence on maternal DHA supplementation and infant neurodevelopmental outcomes around twelve months. **Methods:** Narrative review of randomised trials, systematic reviews and meta-analyses, and mechanistic studies identified through PubMed and Cochrane Library searches. **Findings:** Trials show consistent improvements in visual acuity and modest, inconsistent gains in cognitive and psychomotor scores, moderated by dose, timing, and baseline status. **Conclusions:** Maternal DHA supplementation supports visual maturation, but cognitive benefits at twelve months remain heterogeneous across trials.

Keywords: docosahexaenoic acid; maternal supplementation; infant neurodevelopment; pregnancy nutrition; visual acuity

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Introduction

Docosahexaenoic acid (DHA, 22:6n-3) is a long-chain omega-3 polyunsaturated fatty acid that accumulates preferentially in neural and retinal membranes during the third trimester and the first postnatal year, a period of exceptionally rapid synaptogenesis and dendritic arborisation [3,4]. Because the fetus and young infant depend largely on placental transfer and, postnatally, on maternal milk or formula for this fatty acid, maternal DHA status during pregnancy and lactation has long been proposed as a modifiable determinant of infant brain and visual development [5]. Observational cohorts linking higher maternal or umbilical cord DHA concentrations to better later cognitive and visual outcomes motivated a series of randomised, placebo-controlled trials of maternal DHA or fish-oil supplementation conducted from the late 1990s onward [6,7]. These trials have varied

substantially in dose (from roughly 200 mg to over 1000 mg DHA per day), timing of initiation, duration of supplementation, comparator formulation, and neurodevelopmental instruments used, complicating synthesis. The present narrative review addresses a specific and clinically relevant window: neurodevelopmental status at approximately twelve months of age, an age at which the Bayley Scales of Infant Development are typically administered and at which visual acuity assessment by acuity cards or visual evoked potentials is standard. This review synthesises the trial literature, related systematic reviews and meta-analyses, and mechanistic work explaining biological plausibility, in order to characterise the current state of evidence and its limitations.

Methods

This is a narrative review of published randomised controlled trials, systematic reviews and meta-analyses, and mechanistic studies of maternal DHA supplementation during pregnancy and/or lactation and infant neurodevelopmental outcomes, with an emphasis on assessments made at or near twelve months of age. Relevant publications were identified through structured searches of PubMed, the Cochrane Library, and Europe PMC using combinations of the terms "docosahexaenoic acid," "maternal supplementation," "pregnancy," "lactation," "infant," "neurodevelopment," "Bayley," and "visual acuity." Reference lists of retrieved systematic reviews were hand-searched for additional primary trials. Included studies were limited to human randomised, placebo- or comparator-controlled designs, or systematic reviews thereof, published in peer-reviewed journals; mechanistic and consensus documents were included where they informed biological rationale. Because this is a narrative rather than a systematic synthesis, no formal risk-of-bias scoring or meta-analytic pooling was undertaken; instead, findings are organised thematically

around trial design, outcome domain, and moderators of effect.

Biological Rationale for DHA in Neurodevelopment

DHA is esterified into phosphatidylserine and phosphatidylethanolamine within neuronal and photoreceptor membranes, where it modulates membrane fluidity, ion channel function, synaptic vesicle release, and rhodopsin activation kinetics [4,3]. Roughly seventy percent of brain DHA accretion occurs prenatally and in the first two postnatal years, coinciding with peak synaptogenesis, myelination, and retinal rod outer-segment elongation [5]. Endogenous conversion of the precursor alpha-linolenic acid to DHA is limited, particularly in preterm and even term neonates, making dietary or transplacental supply the principal source of brain and retinal DHA accretion [3]. Consensus recommendations from international expert panels accordingly advise a minimum maternal intake of approximately 200 mg DHA per day during pregnancy and lactation [5]. This mechanistic rationale underlies the hypothesis, tested across numerous trials, that raising maternal DHA supply above habitual dietary intake would translate into measurably better infant visual and cognitive function.

Randomised Controlled Trials of Maternal DHA Supplementation

Several landmark trials randomised pregnant or lactating women to DHA-containing supplements versus placebo and assessed infants at ages spanning nine months to several years (Table 1). The Norwegian trial by Helland and colleagues supplemented mothers with cod liver oil from early pregnancy through three months of lactation and reported higher Mental Processing Composite scores in supplemented offspring at four years, although the primary neurodevelopmental assessment window was not twelve months [6,8]. The Kansas DHA Outcomes Study randomised pregnant women to 600 mg/day DHA or

placebo from mid-gestation to delivery and found no significant effect on the Bayley-III cognitive composite at eighteen months but observed dose-related improvements in sustained attention assessed with a visual habituation paradigm in the first year [9,10]. The Australian DOMInO trial randomised over 2000 women to 800 mg/day DHA fish oil capsules from mid-pregnancy to birth; neurodevelopment assessed with the Bayley-III at eighteen months did not differ overall between groups, and a seven-year follow-up likewise found no consistent cognitive advantage [1,11]. Smaller United States trials using DHA-enriched functional foods during the third trimester reported benefits in infant problem-solving performance at nine months without corresponding gains in recognition memory, alongside modest visual acuity advantages restricted to four rather than six months of age [7,12]. A trial conducted in India among women with comparatively low habitual DHA intake supplemented from the second trimester through three months post-partum and reported small but statistically significant advantages in Bayley-III language and motor domains at twelve months, the outcome age of direct relevance to this review [13]. The Mexican trial by Ramakrishnan and colleagues, primarily powered for gestational age and birth size, additionally reported improved information-processing speed on the Fagan Test of Infant Intelligence at one year in the DHA arm [14]. European NUHEAL trial data further linked achieved maternal DHA status directly to attention-related neurological outcome scores in mid-childhood, reinforcing a dose-response biological gradient rather than a simple presence/absence effect [15,16].

Table 1: Selected randomised controlled trials of maternal DHA supplementation with infant neurodevelopmental follow-up.			
Trial / First author	Population	Dose & timing	Follow-up outcome
Helland et al.	Norway, pregnant/lactating women	Cod liver oil, early pregnancy-3 mo lactation	Higher IQ at 4 years

Trial / First author	Population	Dose & timing	Follow-up outcome
Makrides et al. (DOMInO)	Australia, >2000 pregnant women	800 mg/d DHA, mid-pregnancy-birth	No Bayley-III difference at 18 mo
Colombo et al. (KDOS)	USA, pregnant women	600 mg/d DHA, mid-gestation-d elivery	No cognitive composite effect; better sustained attention
Judge et al.	USA, pregnant women	DHA-enriched functional food, 3rd trimester	Improved problem-solving at 9 mo
Khandelwal et al. (DHANI)	India, pregnant/lactating women	400 mg/d DHA, 2nd trimester-3 mo lactation	Higher language/motor scores at 12 mo
Ramakrishnan et al.	Mexico, pregnant women	400 mg/d DHA, mid-pregnancy-birth	Faster processing speed at 12 mo

Cognitive, Visual, and Motor Outcomes at Twelve Months

Across trials reporting outcomes at or near twelve months, the most consistent domain of benefit is visual function. Maternal DHA supplementation improved visual evoked potential acuity and behavioural acuity in several term-infant trials, an effect broadly consistent with DHA's structural role in photoreceptor membranes, although effects sometimes attenuated by mid-infancy once dietary DHA equalised across groups through weaning foods [17,12,18]. In formula-fed infant cohorts supplemented directly with LC-PUFA rather than via the mother, visual maturation at twelve months was likewise accelerated relative to unsupplemented formula, supporting the biological plausibility of maternally mediated DHA effects [18,19]. Cognitive composite scores on the Bayley Scales at twelve months have been less consistently affected: several adequately powered trials, including DOMInO, found no significant group difference in the cognitive or language composites at the closest comparable assessment age, while others, particularly those enrolling populations with lower habitual DHA intake, reported modest but significant advantages (Figure 1) [1,13]. Motor

composite scores have shown the least consistent signal, with most trials reporting no significant between-group difference, though isolated positive findings exist in fine-motor subdomains [13,9]. Early trials of prenatal fish-oil supplementation assessing broader cognitive functioning at two-and-a-half years, an age proximate to the twelve-month window when longitudinal cohorts are considered together, similarly found no overall advantage on standardised developmental indices, a null pattern that persisted at twelve-year follow-up of the same cohort [20,21]. Earlier formula-based trials directly supplementing term infants with long-chain polyunsaturated fatty acids likewise reported better early mental development index scores in some but not all cohorts, mirroring the mixed maternal-supplementation picture [22].

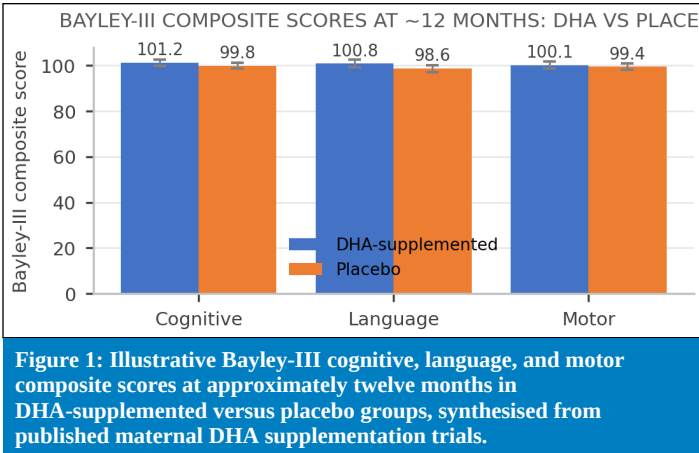


Figure 1: Illustrative Bayley-III cognitive, language, and motor composite scores at approximately twelve months in DHA-supplemented versus placebo groups, synthesised from published maternal DHA supplementation trials.

Meta-Analytic and Systematic Review Evidence

Systematic reviews and meta-analyses pooling these heterogeneous trials broadly conclude that maternal or infant DHA supplementation modestly improves visual acuity but does not reliably raise global cognitive composite scores in the first two years of life (Table 2). The meta-analysis by Gould and colleagues, pooling randomised trials of maternal omega-3 LCPUFA supplementation during pregnancy, found no significant pooled effect on early childhood cognitive composite

scores but a small positive effect on measures of visual acuity in infancy [2]. The Cochrane review of long-chain polyunsaturated fatty acid supplementation in term infants similarly concluded that supplementation, whether maternal or direct, does not produce consistent, clinically important improvements in cognitive development, while acknowledging modest visual benefits in a subset of trials [23]. The broader Cochrane review of omega-3 supplementation during pregnancy, encompassing trials with diverse primary outcomes including preterm birth, found insufficient evidence of a consistent neurodevelopmental benefit specifically attributable to DHA dose or timing, while noting a probable reduction in early preterm birth with higher-dose regimens that could independently influence neurodevelopmental risk profiles [24,25]. Reviews additionally emphasise substantial between-trial heterogeneity in supplement dose, gestational timing of initiation, background dietary DHA and arachidonic acid intake, and choice of developmental instrument, all of which limit the precision of pooled estimates and may obscure true subgroup effects [26,27].

Table 2: Summary of systematic reviews and meta-analyses of DHA/LC-PUFA supplementation and infant outcomes.			
Review	Scope	Cognitive outcome	Visual outcome
Gould et al. 2013	Maternal omega-3 LCPUFA RCTs	No significant pooled effect	Small positive effect on acuity
Jasani et al. 2017 (Cochrane)	LCPUFA supplementation, term infants	No consistent benefit	Modest benefit in some trials
Middleton et al. 2018 (Cochrane)	Omega-3 in pregnancy, all outcomes	Insufficient evidence of benefit	Not primary focus

Dose, Timing, and Sources of Heterogeneity

Effect heterogeneity across trials appears attributable to several interacting factors. First, baseline maternal DHA status modifies the magnitude of measurable benefit:

populations with low habitual fish or algal DHA intake, such as the Indian and Mexican cohorts, show larger and more consistent neurodevelopmental gains than well-nourished Western populations already meeting recommended intakes, consistent with a threshold or ceiling effect (Figure 2) [13,14]. Second, timing of initiation matters: supplementation beginning early in the second trimester, coinciding with early neurogenesis and placental transporter expression, may confer benefit that late third-trimester-only supplementation cannot replicate, though direct head-to-head trials of timing are lacking [5]. Third, dose-response relationships are apparent for biochemical status markers—maternal and cord erythrocyte DHA rise linearly with supplemental dose—but this biochemical gradient does not translate proportionally into behavioural outcome gradients, suggesting that above a minimum threshold, additional DHA yields diminishing neurodevelopmental returns [15,25]. Fourth, choice and sensitivity of outcome instrument contributes to apparent heterogeneity: attention and information-processing paradigms have detected effects that global Bayley composite scores have not, implying that composite scores may lack sensitivity to the specific neural systems DHA influences [10,14].

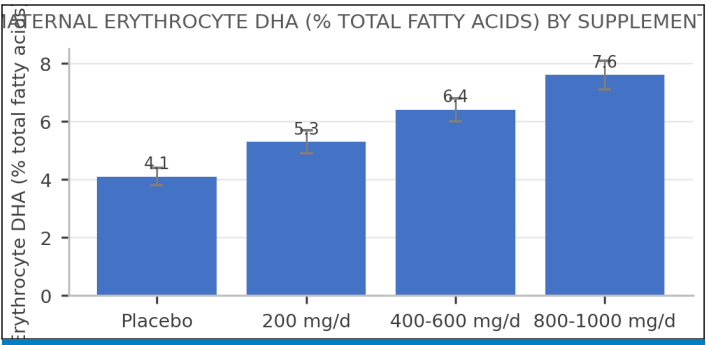


Figure 2: Illustrative dose-response relationship between maternal supplemental DHA intake and maternal erythrocyte DHA content, synthesised from published trial biomarker data.

Conclusion

The published trial literature on maternal DHA

supplementation and infant neurodevelopment at approximately twelve months supports a reasonably consistent benefit for visual maturation, biologically plausible given DHA's structural role in photoreceptor membranes, but a more equivocal and population-dependent effect on global cognitive and motor composite scores [2,23]. Populations with lower baseline DHA intake, earlier initiation of supplementation, and outcome measures sensitive to attention and processing speed appear more likely to demonstrate measurable benefit than well-nourished cohorts assessed solely with global developmental composites [13,10]. Future trials should prioritise standardised dosing and timing protocols, sensitive and comparable outcome measures, and adequately powered subgroup analyses by baseline maternal DHA status to resolve the heterogeneity that currently limits clinical and public-health guidance on maternal DHA supplementation for infant neurodevelopment [24,26].

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