

Current Information and Asian Perspectives on Long-Chain Polyunsaturated Fatty Acids in Pregnancy, Lactation, and Infancy: Systematic Review and Practice Recommendations from an Early Nutrition Academy Workshop

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Key Words

Arachidonic acid · Eicosapentaenoic acid · Docosahexaenoic acid · Polyunsaturated fatty acids · Nutrition in pregnancy · Perinatal nutrition · Infant feeding

Abstract

The Early Nutrition Academy supported a systematic review of human studies on the roles of pre- and postnatal long-chain polyunsaturated fatty acids (LC-PUFA) published from 2008 to 2013 and an expert workshop that reviewed the information and developed recommendations, considering particularly Asian populations. An increased supply of n-3

LC-PUFA during pregnancy reduces the risk of preterm birth before 34 weeks of gestation. Pregnant women should achieve an additional supply ≥ 200 mg docosahexaenoic acid (DHA)/day, usually achieving a total intake ≥ 300 mg DHA/day. Higher intakes (600–800 mg DHA/day) may provide greater protection against early preterm birth. Some studies indicate beneficial effects of pre- and postnatal DHA supply on child neurodevelopment and allergy risk. Breast-feeding is the best choice for infants. Breast-feeding women should get ≥ 200 mg DHA/day to achieve a human milk DHA content of $\sim 0.3\%$ fatty acids. Infant formula for term infants should contain DHA and arachidonic acid (AA) to provide 100 mg DHA/day and 140 mg AA/day. A supply of 100 mg DHA/day

should continue during the second half of infancy. We do not provide quantitative advice on AA levels in follow-on formula fed after the introduction of complimentary feeding due to a lack of sufficient data and considerable variation in the AA amounts provided by complimentary foods. Reasonable intakes for very-low-birth weight infants are 18–60 mg/kg/day DHA and 18–45 mg/kg/day AA, while higher intakes (55–60 mg/kg/day DHA, ~1% fatty acids; 35–45 mg/kg/day AA, ~0.6–0.75%) appear preferable. Research on the requirements and effects of LC-PUFA during pregnancy, lactation, and early childhood should continue.

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Introduction

Essential polyunsaturated fatty acids (PUFA) of the omega-3 (n-3) and omega-6 (n-6) series are of critical importance during early life, and they are known to play an essential role in growth and development. Intakes in pregnancy and early life are thought to affect the quality of growth and neurological and immune function in later life.

The long-chain PUFA (LC-PUFA) eicosapentaenoic acid (EPA; n-3) and docosahexaenoic acid (DHA; n-3), and arachidonic acid (AA, n-6), can be formed from the precursors α -linolenic acid (n-3) and linoleic acid (n-6), respectively. However, the rates of conversion of the precursor PUFA are low and are estimated to range from only 0.1 to 10% [1–3]. Moreover, the conversion rates depend on common polymorphisms in the fatty acid desaturase (*FADS*) gene cluster [4, 5]. Pregnant and breastfeeding women with the less common genotypes have a very low ability to form EPA and DHA from ALA and AA from LA, respectively [6–8]. Conversion rates of precursor PUFA in infants, and particularly in premature infants, have been reported as insufficient to allow for biochemical and functional normality [9, 10].

Information on the roles of LC-PUFA during pregnancy, lactation, and infancy was reviewed and intake recommendations were provided in 2007 and 2008 [11, 12]. Since then, many new studies and meta-analyses have provided new information on the role of LC-PUFA in maternal and infant nutrition and on their impact on health and development. Therefore, the Early Nutrition Academy (ENA) decided to have the recent information systematically reviewed, and recommendations for practice were derived by experts in PUFA, perinatal nutrition, and health, taking into account particularly the dietary intake and conditions of Asian populations. The ENA is

a nonprofit society created by and representing the partners of international research projects funded by the European Commission and the Australian National Health and Medical Research Council that perform research on food and dietetic products in pregnancy and early childhood, in part also in collaboration with commercial partners (e.g. www.project-earlynutrition.eu and www.nutrimenhe.eu). The ENA aims to promote knowledge of human nutrition in early life, to stimulate quality research in this and related areas of science, nutrition, and health, and to disseminate such knowledge.

Methods

We performed a systematic search of the literature databases of PubMed using the following search strings: (unsaturated fatty acids OR omega 3 fatty acids OR fish oils OR long-chain omega-3 fatty acids OR docosahexaenoic acids OR omega-6 fatty acids OR arachidonic acid) AND (pregnant women OR pregnancy OR lactating women OR breastfeeding OR lactation OR infants OR infancy).

The search was limited to studies in humans, published during the last 5 years (September 2008 to September 2013), in the English language and reporting functional outcomes. All systematic reviews, meta-analyses, and randomized controlled trials (RCT), were included. In addition, we also evaluated relevant observational studies. Studies that included interventions with essential fatty acids combined with micronutrients in lipid-based supplements or in fat-based flour, meant to be added to homemade meals, were not included in this review despite the fact that a number of these studies reported benefits for children's growth and development [13, 14]. In addition, further relevant publications identified by the group of participating experts were considered. An expert workshop was hosted by the ENA in Singapore prior to the 8th World Congress on Developmental Origins of Health and Disease (DOHaD) in November 2013. Participants were invited based on their expertise in the areas of PUFA, perinatal nutrition, and health, while a focus was placed on experts from Asian countries. At the workshop, the evidence was reviewed and discussed in detail. All conclusions and recommendations presented in this manuscript were agreed upon by consensus.

Results

A total of 20 systematic reviews and/or meta-analyses and 78 original reports of RCT that met the inclusion criteria were found in the systematic literature review. These 78 original reports related to 44 individual studies (13 in pregnant women, 6 in pregnant and lactating women, 2 in lactating women, 3 in preterm infants, 14 in term infants, and 6 in older infants) and are summarized in tables 1–5.

Table 1. Design of all of the RCT included

References	Location	n	Population	Duration	Intervention	Measurements
<i>Pregnancy and lactation</i>						
Lee et al. [67], Stein et al. [34, 155], Imhoff-Kunsch et al. [58], Ramakrishnan et al. [15]	Mexico	1,094	Pregnant women	From 18-22 weeks gestation until delivery	I: daily 400 mg algae DHA; C: placebo	Birth outcomes, infant growth, infant morbidity, cognition, methylation levels
Mozurkewich et al. [69]	USA	126	Pregnant women at risk for depression	From early pregnancy	I: EPA-risk fish oil (1,060 mg EPA + 274 mg DHA), or DHA-rich fish oil (900 mg DHA + 180 mg EPA); C: soy oil placebo	Maternal depression
Gustafson et al. [36]	USA	67	Pregnant women	From 14.4 (+/-4) weeks gestation	I: 600 mg DGA/day; C: placebo oil capsules	Fetal heart rate; infant neurodevelopment
Carlson et al. [22]	USA	350	Pregnant women	From <20 weeks gestation to birth	I: DHA capsules; C: placebo capsules	Pregnancy outcomes
Urwin et al. [50], Noakes et al. [51], Miles et al. [156], Garcia- Rodriguez et al. [81]	UK	123	Pregnant women with low fish consumption	From 20 weeks gestation to delivery	I: consume 2 portions of salmon/week; C: habitual diet	Markers of oxidative stress, umbilical FA status, neonatal immune response and atopy markers; immune factors
Zhou et al. [26], Palmer et al. [55], Makrides et al. [24], Smithers et al. [35]	Australia Domino trial	2,399	Pregnant women, singleton pregnancies	<21 weeks gestation to birth	I: DHA-rich fish oil capsules (800 mg/day DHA); C: matched vegetable oil capsules, no DHA	Maternal depression, neurodevelopment; infant allergies; gestational diabetes, pre-eclampsia; early visual development
Rytter et al. [77-79], Olsen et al. [57]	Denmark	533 enrolled; 523 followed-up	Pregnant women	30 weeks gestation to delivery	I: fish oil capsules (2.7 g n-3 PUFA); C1: olive oil capsules; C2: no capsules	At 19 years of age: blood pressure, heart rate, plasma lipids, lipoprotein, adiposity. Asthma until 16 years of age
Judge et al. [37], Courville et al. [23]	USA	48	Pregnant women	24 weeks gestation to delivery	I: cereal-based functional food with 300 mg DHA for 5 days/ weeks; C: placebo bar	Infant sleep patterning, intra-uterine growth; umbilical blood insulin
Campoy et al. [32]	Spain, Germany, Hungary		Pregnant women	20th weeks gestation to delivery	I: 2 x 2 design; daily supplement with fish oil with or without folate. In addition infants from fish oil mothers received formula with 0.5% DHA and 0.4% AA until 6 months of age; C: placebo supplement during pregnancy, no DHA in formula	Cognition (KABC) at 6.5 years of age
Harper et al. [25]	USA	852	Pregnant women with singleton pregnancy and history of prior spontaneous singleton preterm birth	From 16-22 weeks gestation until 36 weeks gestation	I: daily omega-3 supplement (1,200 mg EPA + 800 mg DHA); C: placebo supplement	Preterm birth

Table 1. (continued)

References	Location	n	Population	Duration	Intervention	Measurements
Su et al. [16]	China	36	Pregnant women with major depressive disorder	For 8 weeks during pregnancy	I: omega-3 PUFA supplement (3.4 g/day); C: placebo supplement	Perinatal depression
Franke et al. [80]	Germany	270	Pregnant women	From 22 weeks gestation	I: 2 × 2 design; daily supplement with fish oil with or without folate. C: placebo supplement	Oxidative stress markers during pregnancy and at delivery
Warstedt et al. [54]	Sweden	145	Pregnant women with allergic disease in immediate family	From 25th week gestation	I: daily 2.7 g n-3 LCPUFA; C: 2.8 g soybean oil	Maternal immune response
Much et al. [21], Hauner et al. [71]	Germany	208	Pregnant women	From the 15th weeks of gestation until 4 months lactation	I: 1,200 mg n-3 LC-PUFA + dietary counseling to reduce the AA intake; C: habitual intake	Birth weight, growth, and body composition at 1 year; adipose tissue growth
van Goor et al. [39], Doornbos et al. [70]	The Netherlands	119	Pregnant women	From the 16th week of gestation until 3 months postpartum	I: supplement with 220 mg DHA/day or 220 mg DHA + AA/day; C: placebo supplement	Neurodevelopment, depressive symptoms
Granot et al. [60]	Israel	60	Pregnant women in their 4th pregnancy or beyond	From the 12th week of gestation until 4 months postpartum	I: 400 mg DHA/day; C: placebo capsules	Infant immune response
Furuhjelm et al. [52, 56, 59]	Sweden	145	Pregnant women at risk of having an allergic infant	From the 25th week of gestation until 3.5 months of breast-feeding	I: 1.6 g EPA + 1.1 g DHA/day; C: placebo	Allergy
Helland et al. [40]	Norway	143	Pregnant women	From the 18th week of gestation until 3 months after delivery	I: 10 ml cod liver oil/day; C: corn oil	Cognition (KABC) at 7 years, BMI at 7 years
Linnamaa et al. [61]	Finland	313	Pregnant women and their infants	From 8th to the 16th week of gestation until cessation of breast-feeding; then infants were supplemented until 2 years of age	I: black currant seed oil (high in omega-6 and omega-3); C: olive oil	Atopic dermatitis
Cheatham et al. [44], Asserhoj et al. [76]	Denmark	122	Lactating women	During the first 4 months of lactation	I: 1.5 g n-3 PUFA oil/day (fish oil); C: olive oil	Cognition at 7 years (processing speed, stroop task, strengths and difficulties questionnaire); blood pressure, anthropometry, diet, and physical activity at 7 years of age
<i>Term infants</i> Colombo et al. [89, 107]	USA	122	Term infants followed up to 6 years of age	From birth to 12 months	I: DHA 0.32; 0.64 or 0.96% of total fatty acids; C: 0.00% DHA	Behavioral and indices of attention at 4, 6, and 9 months of age; longitudinal cognitive change from 18 months until 6 years every 6 months

Table 1. (continued)

References	Location	n	Population	Duration	Intervention	Measurements
Willatts et al. [90]	UK	71 LC-PUFA, 76 control, 88 breast-fed	Term infants measured at 6 years of age	From birth for 4 months	I: formula with DHA + ARA; C: formula with no LC-PUFA; reference breastfed group	Assessments of IQ; attention control, and speed of processing
de Jong et al. [91, 99, 157]	The Netherlands	169 standard formula, 146 LC-PUFA formula, 159 control	Term infants measured at 9 years of age	The first 2 postnatal months	I: formula with LC-PUFA (0.45% AA and 0.30% DHA); C: standard formula, no DHA	Cognition and behavior, neurological condition, CVD risk, and anthropometry at 9 years
D'Vaz et al. [102, 104], Meldrum et al. [87]	Australia	420	Term infants with a high atopic risk	From birth to 6 months	I: daily supplement of fish oil (280 mg DHA, 110 mg EPA); C: olive oil	Eczema, food allergy, asthma and sensitization; cellular immune function, BSID-III and Child Behavior Checklist, language assessment
Drover et al. [85, 92]	Canada	182	Healthy term infants assessed at 18 months and 2.5 years	From 1–9 days of age until 12 months	I: formula with 0.64% AA and 0.32 or 0.64 or 0.96% DHA; C: 0% DHA	BSID-III at 18 months; Bracken Basic Concept Scale-Revised (school readiness) at 2.5 years
Vivatvakin et al. [95]	Thailand	144	Healthy term infants	From 30 days to 4 months of age	I: whey-based formula with LC-PUFA and oligosaccharides; C: casein-predominant formula	Growth parameters and health (morbidity by recall), gastric emptying and intestinal transit time; bacterial analysis of stool samples
Rzehak et al. [96]	Germany		Full-term infants	From week 4 to month 7	I: formula with canola oil; C: formula without canola oil	Growth (weight, length, and weight and length gain)
Westerberg et al. [158]	Norway	92	Very-low-birth-weight infants	From 1 week after birth until discharge from the hospital (9 weeks on average)	I: human milk with 0.5 ml oil (32 mg DHA and 31 mg AA) per 100 ml; C: human milk with 0.5 ml oil (placebo) per 100 ml	BMDI; Ages and Stages questionnaire at 20 months
Field et al. [101]	Canada		Formula-fed term infants	From ≤14 days of age until 16 weeks of age	I: formula with LC-PUFA; C: standard term formula	Blood immune parameters at 16 weeks of age
Birch et al. [86, 103]	USA	343 (visual acuity), 89 (immune allergies)	Term infants	From 1–9 days of age until 12 months	I: formula with 0.64% AA and 0.32 or 0.64 or 0.96% DHA; C: 0% DHA	Allergies, respiratory diseases, visual acuity
Drover et al. [159]	USA	229	Term infants	From 1–5 days of age (12 months of feeding) or following 6 weeks (6 weeks of feeding) or 4–6 months of breastfeeding (4–6 months' weaning study)	I: formula with DHA and AA; C: control formula	Cognitive function at 9 years
Lamkjaer et al. [98]	Denmark	83	Healthy term infants	Birth to 12 months?	2 × 2 design: I: whole milk with/without fish oil; C: formula with/without fish oil	Anthropometry, IGF-I concentrations, and diet
Gibson et al. [97]	Australia	142	Term infants	From birth until 7 months	I: formula containing LC-PUFA and AA and probiotic <i>B. lactis</i> ; C: unsupplemented formula	Weight gain, length gain, head circumference, immune response at 7 months of age

Table 1. (continued)

References	Location	n	Population	Duration	Intervention	Measurements
Agostoni et al. [88]	Italy	1,160	Healthy infants	From birth throughout the first year of life	I: supplementation with 20 mg liquid DHA; C: placebo supplement	Time of achievement of 4 gross motor milestones
<i>Preterm infants</i>						
Atwell et al. [116], Manley et al. [117], Collins et al. [118], Smithers et al. [121, 124], Makrides et al. [137]	Australia – DINO trial	657	Preterm infants <33 weeks of gestation	From day 2–4 of life until the term-corrected age	I: high DHA milk (1% of total fatty acids) + AA 0.5%; C: standard DHA (0.2–0.3%) + AA 0.5%	Infant fatty acid status, neurodevelopment, visual acuity, language and behavior, growth, atopic respiratory infections, respiratory hospitalizations
Isaacs et al. [122], Kennedy et al. [126]	UK	107	Preterm infants <35 weeks of gestation with a birth weight <2,000 g	From birth until 9 months of age	I: LC-PUFA supplemented formula with 0.5% DHA; C: unsupplemented formula	Cognition at 10 years of age, growth and blood pressure at 10 years of age
Henriksen et al. [123]	Norway	143	Very preterm infants with a birth weight <1,500 g	From 1 week after birth until discharge from the hospital (on average at 9 weeks of life)	I: supplementation with 32 mg DHA + 31 mg AA; C: no supplementation	Cognitive development at 6 months of age
<i>Older infants</i>						
van der Merwe et al. [109]	Gambia	172	Infants aged 3–9 months	6 months (from 3 to 9 months of age)	I: 200 mg DHA + 300 mg EPA oil/day; C: 2 ml olive oil/day	Gut integrity (urinary lactulose:mannitol ratio and intestinal mucosal inflammation by fecal calprotectin), growth, morbidity, cognition (2-step means-end test and attention assessment)
Andersen et al. [110, 111]	Denmark	133	Infants aged 9–18 months	12 months (from 9 to 18 months of age)	I: 5 ml fish oil/day; C: 5 ml sunflower oil/day	Fecal microbiota (measured by terminal restriction fragment length polymorphism), growth and skinfold thickness
Ayer et al. [112]	Australia	616	Infants/children from the time of weaning until 5 years of age	5 years (from weaning until 5 years of age)	I: active diet interventions to increase n–3 and decrease n–6 intakes; C: no diet interventions	Blood pressure and arterial structure at 8 years of age
Lauritzen et al. [113]	Denmark	83	Infants aged 9–12 months	3 months (from 9 to 12 months of age)	2 × 2 design: I: 3.4 ml fish oil with cow's milk or formula; C: no fish oil	Heart rate and erythrocyte fatty acid composition
Schwartz et al. [160]	Germany	102	Term infants	From 4 to 10 months of age	I: commercial complementary meals with rapeseed oil (1.6 g/meal) rich in ALA; C: commercial complementary meals with corn oil (3.4 g/meal) rich in n–6	Plasma fatty acid concentrations
BMIDI = Bayley Mental Development Index; C = control; I = intervention.						

Table 2. Outcomes of RCT in pregnant and lactating women

Reference	Outcomes					other	conclusion
	pregnancy outcomes	infant/child cognition	postnatal growth	infant/child allergy and immunity	epigenetics, markers of CVD	maternal depression	
Lee et al. [67], Stein et al. [34, 155], Imhoff-Kunsch et al. [58], Ramakrishnan et al. [15]	No difference was seen in gestational age or birth outcomes overall. However, children from supplemented primigravida women had an increased birth weight and a larger head circumference than controls.	No effects on auditory evoked responses at 1 and 3 months or visual evoked potentials at 3 and 6 months were seen.	An increased length at 18 months of age was observed in the supplemented group of children born to primigravida women only.	A decreased occurrence of common colds at 1 month of age and a shorter duration of common respiratory illnesses at 1, 3, and 6 months of age were observed in the DHA-supplemented group.	Supplementation modulated global methylation levels and the Th1/Th2 balance, important for the prevention of inflammatory disorders.		Birth weight: + (primigravida only), cognition: no effect, growth: + (primigravida only), morbidity: +, methylation: +
Mozurkewich et al. [69]						No differences between groups on any of the depressive symptom scales at 26–28 weeks of gestation, 34–36 weeks of gestation, or 6–8 weeks postpartum were seen.	Maternal depression: no effect
Gustafsson et al. [36]	The fetal heart rate variability and newborn neurobehavior in autonomic and motor clusters were significantly higher in the DHA-supplemented group.						Fetal heart rate and early newborn neurodevelopment: +
Carlson et al. [22]	A longer gestation duration and a greater birth length and head circumference were observed in the DHA-supplemented group; fewer preterm births were seen in the DHA-supplemented group.						Birth outcomes: +

Table 2. (continued)

Reference	Outcomes	pregnancy outcomes	infant/child cognition	postnatal growth	infant/child allergy and immunity	epigenetics, markers of CVD	maternal depression	other	conclusion
Urwin et al. [50], Noakes et al. [51], Miles et al. [156], García-Rodríguez et al. [81]					The intervention group showed improvements in neonatal immune response markers but no difference in atopy markers at 6 months of age. Lower IgA levels in breast milk were observed in the intervention group.			No difference in oxidative stress markers were seen; there were higher EPA and DHA plasma concentrations in the intervention group; there were higher EPA and DHA concentrations in breast milk in the intervention group.	Immune response: +/-, oxidative stress: no impact
Zhou et al. [26], Palmer et al. [55], Makrides et al. [24], Smithers et al. [35]	No differences in birth weight, length, or head circumference were seen; no difference in the risk of gestational diabetes or preeclampsia was observed; there was a suggestion of a reduced risk of perinatal death and neonatal convulsions in the intervention group.	No differences between groups in visual acuity at 4 months of age were observed; no differences between groups in mean BSID scores (cognitive and language development) at 18 months of age were seen.			No differences in IgE-associated allergies in the first year of life were seen, but the supplemented group had lower atopic eczema and egg sensitization.		No differences between groups in depressive symptoms during the first 6 months postpartum were observed.		Birth outcomes: no impact, suggestion for perinatal deaths?; cognition: no impact, allergies: +/-, depression: no impact
Rytter et al. [77–79], Olsen et al. [57]					The hazard of asthma until 16 years of age was reduced by 63%; the hazard of allergic asthma was reduced by 87% in the intervention group.	No differences in adiposity, plasma lipids and lipoproteins, blood pressure, heart rate, or heart rate variability at 19 years of age were observed.			Allergies: +, early markers of CVD: no impact
Judge et al. [37], Courville et al. [23]	A lower ponderal index at birth was seen in the intervention group; there were no differences in birth weight or length.	There were fewer arousals in quiet and active sleep in the intervention group, suggesting a beneficial impact on infant sleep organization.			There were lower umbilical cord blood insulin concentrations in the intervention group.				Early markers of CVD/adiposity: +, sleep patterns as markers of neurodevelopment: +

Table 2. (continued)

Reference	Outcomes						conclusion
	pregnancy outcomes	infant/child cognition	postnatal growth	infant/child allergy and immunity	epigenetics, markers of CVD	maternal depression	other
Campoy et al. [32]		There were no differences in KABC scores at 6.5 years between intervention groups.					Cognition: no impact
Harper et al. [25]	No difference in the risk of preterm delivery was observed (RR 0.91).						Preterm delivery: no impact
Su et al. [16]						The intervention group had significantly lower depression scores at 6 weeks and at the end of the study.	Depression: +
Franke et al. [80]							There were no differences between groups in oxidative stress markers during pregnancy or at delivery.
Warstedt et al. [54]				Decreased prostaglandin E2 production was seen in the intervention group, particularly in the nonatopic mothers, suggesting dampening of immune responses involved in allergic inflammation.			Immune response: +
Much et al. [21], Hauner et al. [71]	Birth weight and birth length were positively related to maternal n-3 LCPUFA and n-6 LCPUFA at 32 weeks of gestation.		Maternal AA and n-6 LC-PUFA were significantly negatively related to the BMI and the ponderal index at 1 year, but there was no association with fat mass; no difference in adipose tissue growth was seen.				Birth outcomes: +, postnatal growth: +?, adipose tissue/fat mass: no impact

Table 2. (continued)

Reference	Outcomes	pregnancy outcomes	infant/child cognition	postnatal growth	infant/child allergy and immunity	epigenetics, markers of CVD	maternal depression	other	conclusion
van Goor et al. [39], Doornbos et al. [70]			At 18 months of age, there was no impact on the BSID mental development index; no impact on the index for minor neurological dysfunction was observed.				No difference in peripartum depressive symptoms between groups were seen.		Cognition: no impact, maternal depression: no impact
Granot et al. [60]					A higher percentage of CD4 naive cells and decreased CD4 and CD8 IFN production, compatible with a weaker proinflammatory response, were observed.				Immune response: suggestion of a negative impact
Furuhjelm et al. [52, 56, 59]					A lower prevalence of food allergy in infants in the supplemented group was seen; no benefits for the prevalence of clinical symptoms of allergic disease were observed, but there was a decrease in the cumulative incidence of IgE-associated diseases throughout the first 2 years of life; lower Th2/Th1 ratios and higher Th1-associated antibody levels were seen, as well as increased IgG titers to diphtheria and tetanus toxins in the supplemented group in nonallergic infants but not in allergic infants.				Immune response: +, particularly in nonallergic infants
Helland et al. [40]			No differences in scores on the KABC at 7 years of age were seen despite the fact that higher IQ scores at 4 years of age had been observed in infants in the cod liver oil group.	No differences in height, weight, or BMI were observed between groups at 7 years of age.					Cognition: no impact, postnatal growth: no impact

Table 2. (continued)

Reference	Outcomes	pregnancy outcomes	infant/child cognition	postnatal growth	infant/child allergy and immunity	epigenetics, markers of CVD	maternal depression	other	conclusion
Linnamaa et al. [61]					There was a lower prevalence of AD in the intervention group at 12 months; there was no difference at 24 months of age.				Immune response: + (but it was not possible to distinguish the effect from omega-3 alone)
Cheatham et al. [44], Asserhoj et al. [76]	Lower scores on speed of processing in the children of supplemented mothers and lower scores on inhibitory control/working memory in children with a higher DHA status at 4 months were observed.			No difference in body composition were seen between groups.		There were higher diastolic and mean arterial blood pressure values in the fish oil-supplemented group among boys only; there was a higher energy intake and lower PAL values in supplemented boys; no difference was seen in girls.			Cognition: – ?, early CVD markers: – (in boys)
Jensen et al. [42]	Higher scores on the sustained-attention subscale at 5 years were observed for children whose mothers received DHA; there was a previously reported better performance of children of DHA-supplemented mothers on tests of psychomotor development at 30 months of age.								Cognition: +
PAL = Physical activity level; + = positive effect; – = negative effect; ? = possible effect, not significant.									

Table 3. Outcomes of RCT in term infants

Reference	Outcomes	growth/anthropometry	allergy/immune function	early markers of CVD	other	conclusion
Colombo et al. [89, 107]	Positive effects on attention were seen for the lower 2 levels of DHA compared to controls, but not for the highest level of DHA; no long-term effects were observed at 18 months, but various positive effects were observed at 3, 5, and 6 years on more specific or fine-grained tasks.					Cognition: +
Willatts et al. [90]	At 6 years of age, children in the LC-PUFA group had better scores on speed of processing; no effects on IQ or attention were observed.					Cognition: +
de Jong et al. [91, 99, 157]	LC-PUFA during infancy was associated with a higher mean verbal IQ at 9 years in children exposed to smoking during pregnancy. LC-PUFA during infancy was associated with lower mean verbal memory scores in children not exposed during pregnancy. Executive function scores were significantly lower in the LC-PUFA group compared to controls. There was no difference between the intervention and control groups in terms of neurological function.	None of the anthropometric measurements (weight, height, head circumference) differed between the formula groups.		None of the cardiovascular measures (blood pressure, heart rate) differed between the formula groups.		Cognition: +/-, CVD risk: no impact
D'Vaz et al. [102, 104], Meldrum et al. [87]	No differences between groups in terms of BSID-III development scores were seen; children in the fish oil group had significantly higher scores on later developing gestures at 12 and 18 months.		No differences between groups in terms of childhood allergic diseases (eczema, asthma) were seen. Lower allergen-specific Th2 responses and elevated polyclonal Th1 responses were observed in the fish oil group, suggesting potentially allergy-protective effects on immune function.			Cognition: no impact, behavior: +?, allergy/immune function: +/-no impact
Drover et al. [85, 92]	No difference in BSID scores between the 4 groups was seen, but when all of the DHA groups were combined higher MDI scores were observed compared to controls. No differences in school readiness or language development, but lower receptive vocabulary scores at 2 years of age, were seen in children consuming 0.32 and 0.96% DHA formula but not 0.64% DHA formula.					Cognition: +, school readiness and language: no impact
Vivatkin et al. [95]		No differences in growth parameters were observed between groups.			The intervention group had fewer hard stools and had data closer to breast-fed infants' stool microbiota composition, gastric transit time, and intestinal transit time compared to controls.	Growth: no difference, gastrointestinal comfort: +

Table 3. (continued)

Reference	Outcomes	growth/anthropometry	allergy/immune function	early markers of CVD	other	conclusion
Rzehak et al. [96]		No differences in growth (weight and length gain) were observed between groups.				Growth: no difference, gastrointestinal comfort: +
Westerberg et al. [158]	No differences in BMDI scores were seen. There were suggestive positive effects of free-play sessions on functions related to attention in the intervention group.					Cognition: no impact, attention: +?
Field et al. [101]			Children in the supplemented group had altered immune parameter responses closer to those in a breast milk-fed control group. Suggesting a hypothetical immune benefit.			Immune response: +
Birch et al. [86, 103]	There were no differences between the 4 intervention groups on visual acuity, but infants in the DHA groups combined had better visual acuity scores than infants in the control group.		Infants in the DHA group had significantly lower odds of developing upper respiratory infections, wheezing/asthma, or any allergy compared to infants in the control group.			Visual acuity: +, immune response: +
Drover et al. [159]	During the 12 months of feeding and 6 weeks of weaning, supplemented children had more successful task completions and higher intention scores (measures of problem solving).					Cognition: +
Lamkjaer et al. [98]		Milk increased IGF-1 in boys but not in girls; no effect of fish oil was seen. There was no effect on growth.				Growth: no effect of fish oil
Gibson et al. [97]		No difference in growth between groups was observed.	No difference in response to vaccines was observed.			Growth: no effect, immune response: no effect
Agostoni et al. [88]	The time to achievement of sitting without support was shorter in the intervention group; however, the significance of this 1-week change remains to be determined. No effects were observed for the other motor milestones.					Motor milestones: no response?

BMDI = Bayley Mental Development Index; ? = possible effect (not significant); + = positive effect; – = negative effect.

Table 4. Outcomes of RCT in preterm infants

Reference	Outcomes	growth/anthropometry	allergy/immune function	early markers of CVD	other	conclusion
Atwell et al. [116], Manley et al. [117], Collins et al. [118], Smithers et al. [121, 124], Makrides et al. [137]	Infant fatty acid status, neurodevelopment, visual acuity, language and behavior, growth, atopic respiratory infections, respiratory hospitalizations	No differences were observed in scores of language development or behavior assessed between 3 and 5 years' corrected age. Overall scores on the BSID did not differ between groups, but girls fed the high-DHA diet had higher MIDI scores at 18 months' corrected age. Visual acuity was higher at 4 months' corrected age in the high-DHA group.	Infants fed DHA were 0.7 cm longer at 18 months' corrected age; Infants in the high-DHA group with a birth weight $\geq 1,250$ g had increased length and weight at 12 and 18 months' corrected age.	No difference in hospitalizations for lower-respiratory tract problems in the first 18 months of life was observed; a reduction in bronchopulmonary dysplasia in boys and in all infants with a birth weight $< 1,250$ g and a reduced incidence of reported hay fever at 12 and 18 months' corrected age were seen.		Cognition: + (in girls), visual acuity: +, growth: +, early CVD: +
Isaacs et al. [122], Kennedy et al. [126]	Cognition at 10 years of age; growth and blood pressure at 10 years of age	No overall effect was seen on any of the cognitive benefits; however, girls in the DHA-supplemented group had higher language scores, and children who only received formula and no breast milk had better IQ and memory scores.	Girls in the supplemented group had a higher body weight and adiposity (measured by skinfold thickness) at 10 years of age; this was not observed in boys.		Girls in the supplemented group had higher systolic and diastolic blood pressure at 10 years of age; this effect was not observed in boys. Together with the adverse effects on adiposity in supplemented girls, this suggests adverse effects on later health.	Cognition: + (in girls), long-term growth: + (in girls), early CVD risk: - (in girls)
Henriksen et al. [123]	Cognitive development at 6 months of age	Better recognition memory and higher problem solving scores at 6 months were observed in infants supplemented with DHA and AA.				Cognition: +
+ = Positive effect; - = negative effect.						

Table 5. Outcomes of RCT in older infants

Reference	Outcomes	growth/anthropometry	allergy/immune function	early markers of CVD	other	conclusion
van der Merwe et al. [109]	No difference in scores between groups was observed.	A significant increase in MUAC at 6 and 12 months of age was seen in the intervention group; at 12 months of age, a significant increase in skinfold thickness was seen in the intervention group; there were no differences in other growth indicators.	No difference in morbidity was seen between groups.		No difference in gut integrity was seen between groups.	Cognition: no impact, UAC: +, linear growth: no impact, morbidity: no impact, intestinal integrity: no impact
Andersen et al. [110, 111]		No differences between groups were observed in any of the anthropometric outcomes, but infants in the intervention group had a lower skinfold ratio at 18 months.			In children who were weaned prior to 9 months of age (prior to the onset of the study) only, reduced concentrations of bp102 and bp100 gut bacteria were observed in the intervention group.	Anthropometry: no impact, skinfold ratio: -, gut microflora: + in early weaned children only
Ayer et al. [112]				No differences in blood pressure, carotid intima media thickness, other arterial structure and function markers, or lipoprotein concentrations were observed.		Early CVD markers: no benefit
Lauritzen et al. [113]				A longer RR interval in fish oil-supplemented boys and in infants with confirmed changes in erythrocyte n-3 PUFA was seen.		Early CVD markers: + in certain subgroups with higher needs
Schwartz et al. [160]					Plasma concentrations of total n-3 fatty acids and n-3 LC-PUFA, but not ALA, were higher in the intervention group, suggesting improved n-3 LCPUFA synthesis.	LCPUFA synthesis: +
MUAC = Mid-upper-arm circumference; UAC = upper-arm circumference; + = positive effect; - = negative effect.						

We evaluated a total of 21 individual studies published since 2008 identified by the systematic search. These studies investigated the impact of n-3 LC-PUFA interventions on pregnancy and longer-term outcomes. Eleven of these studies supplemented with LC-PUFA during pregnancy, 6 studies supplemented both during pregnancy and during lactation, 2 studies supplemented mothers during pregnancy and subsequently the infants after delivery, and 2 studies supplemented during lactation only. In addition, 12 systematic reviews or meta-analyses were found. Two of the studies in pregnant women published since 2008 were performed in women from low- or middle-income countries, i.e. Mexico [15] and China [16].

Pregnancy Outcomes

A systematic review of 15 RCT found that women receiving an additional n-3 LC-PUFA supply in different amounts during pregnancy delivered infants with a slightly higher birth weight (42.2 g; 95% CI 14.8–69.7), with a 26% lower risk of early preterm delivery (<34 weeks) (RR 0.74; 95% CI 0.58–0.94). In addition, supplemented women showed a trend toward a decreased risk of preterm delivery (RR 0.91; 95% CI 0.83–1.02) [17]. Three previous meta-analyses also evaluated such effects. Szajewska et al. [18] reported a significant increase in the mean pregnancy duration of 1.6 days, along with a slight increase in infant size at birth with a nonsignificant trend toward fewer preterm births before 37 weeks of gestation (RR 0.67; 95% CI 0.41–1.10, n.s.). A Cochrane review by Makrides et al. [19] included 6 randomized trials on marine oil supplementation in different amounts during pregnancy, involving 2,783 women. Women allocated to a marine oil supplement had a small but significant increase in the length of gestation of 2.6 days, along with a slightly higher infant birth weight (47 g; 95% CI 1–93). The number of early preterm births before 34 completed weeks of gestation was significantly reduced by marine oil (RR 0.69, 95% CI 0.49–0.99; 3 trials, 2,440 women) [19]. In high-risk pregnancies, n-3 LC-PUFA supplementation showed an even more marked and significant reduction in the number of early preterm births before 34 weeks of gestation (RR 0.39; 95% CI 0.18–0.84) [20].

Three studies published after 2008 confirmed the positive effects of n-3 LC-PUFA interventions during pregnancy on birth-size, with larger birth weights and head circumferences in infants of supplemented mothers [15, 21, 22]. In one of these studies in Mexico, these effects were only seen in firstborn infants [15]. In a small

study of 48 pregnant women who had consumed cereal-based food fortified with DHA, a lower ponderal index but no effect on birth weight or length were reported [23]. Four studies have been published since 2008 reporting on gestational age at birth and the risk of early preterm delivery. Makrides et al. [24] performed a double-blind RCT in 2,399 women with singleton pregnancies supplemented from mid-gestation to birth with DHA-rich fish oil capsules providing 800 mg DHA/day or matched vegetable oil capsules without DHA. The adjusted RR for early preterm birth before 34 weeks of gestation was significantly reduced to 0.49 (95% CI 0.25–0.94; $p = 0.03$), while the mean gestational age was prolonged by 1 day ($p = 0.05$) [24]. Carlson et al. [22] performed a double-blind RCT supplementing women during the second half of pregnancy with 600 mg DHA daily or placebo. Supplementation led to a longer mean duration of gestation by 2.9 days ($p = 0.041$), along with a higher birth weight (plus 172 g; $p = 0.004$), length (plus 0.7 cm; $p = 0.022$), and head circumference (plus 0.5 cm; $p = 0.012$). Early preterm births before 34 weeks of gestation were markedly reduced from 4.8% in controls to 0.6% in the intervention groups ($p = 0.025$), and the length of hospital stay in infants born preterm was shorter (8.9 vs. 40.8 days; $p = 0.026$) [22]. No safety issues occurred. In contrast, 2 other studies that provided lesser amounts of n-3 LC-PUFA did not observe a beneficial effect of supplementation on premature birth [15, 25]. These studies that did not observe a benefit of supplementation were performed in Mexican women and in women with major depressive disorders. Only one study reported on pregnancy complications as an outcome. In Mexico, no impact was found on gestational diabetes and preeclampsia after maternal supplementation with DHA in pregnancy [26].

A cross-sectional study in rural, poor Southern Indian women found a significant positive correlation between EPA/DHA intake during pregnancy and birth weight [27]. Women whose fish intake was in the lowest tertile in the third trimester of pregnancy had a significantly increased adjusted odds ratio for the risk of low birth weight compared to those in the highest tertile, but there was no difference in gestational duration.

In conclusion, the results of 4 meta-analyses and 2 recent large RCT consistently showed a protective effect of n-3 LC-PUFA supplementation during pregnancy with respect to a reduction in the incidence of early preterm births (<34 weeks gestation). The impressive effect sizes of the reductions were 26% in the most recent meta-analysis and 51 and 87.5%, respectively, in 2 more recent large

RCT using higher n-3 LC-PUFA dosages (600 or 800 mg DHA/day). Two other studies found no significant effects. No dose-response studies with direct comparisons of the effects of different dosages on early preterm birth have been performed. However, the greater effect sizes observed in the recent studies using 600–800 mg DHA/day compared to the earlier studies providing lower dosages are suggestive of a possible greater protective effect at higher intake levels, whereas no adverse effects were reported with the higher dosages. n-3 LC-PUFA supplementation in pregnancy also led to a small increase in infant size at birth, whereas there was no evidence of relevant untoward effects. Given that early preterm birth before 34 weeks of gestation markedly increases infant short- and long-term morbidity as well as mortality, it is advisable that pregnant women aim to achieve a regular supply of preformed n-3 LC-PUFA from foods such as oily fish and seafood or from supplements. A regular supply prior to pregnancy may also be beneficial since it contributes to the accumulation of body stores of n-3 LC-PUFA that can be utilized and thus contribute to securing protective blood and tissue levels of n-3 LC-PUFA during pregnancy (and during lactation; see below).

Cognitive and Visual Development

In several observational cohort studies, beneficial effects of n-3 or fish intake during pregnancy and/or lactation on the developmental outcomes and cognition of the offspring up to 14 years of age have been reported, even after adjusting for potential confounding factors [28–30].

However, the findings or outcomes from RCT are conflicting. A meta-analysis of 11 RCT involving 5,277 participants found no significant differences in standardized psychometric test scores for cognitive, language, or motor development in the offspring of mothers who had been supplemented with LC-PUFA during pregnancy [31]. There was a suggestion of higher cognitive development scores at later ages (2–5 years) in children of supplemented mothers derived from 2 trials. No results on visual outcomes could be calculated because of the variety of visual assessments used in the different studies.

Five studies have been published since 2008 evaluating cognitive outcomes and visual acuity after n-3 LC-PUFA supplementation during pregnancy; one of these studies extended the supplementation to the newborns until they reached 6 months of age [32]. Three of these studies did not observe beneficial effects of supplementation on the overall cognitive test scores at 18 months [24] or 6.5 years of age [33], or on visual development at 3–6 or 4 months of age [34, 35]. A study in 67 pregnant women given a

daily supplement of 600 mg DHA/day observed higher fetal heart rate variability measured at 24, 32, and 36 weeks of gestation and higher scores on a newborn neonatal behavioral assessment scale [36]. A study in 48 pregnant women in the USA who consumed cereal-based DHA-fortified food during pregnancy observed fewer sleep arousals in the infants of supplemented women, which the authors identified as an early marker of improved neurodevelopment [37].

Observational studies found a link between LC-PUFA status markers during pregnancy and at birth, reflecting a maternal supply before and during pregnancy, and later neurodevelopmental outcomes. Steer et al. [8] explored the link between maternal red blood cell contents of LC-PUFA in pregnancy and children's IQ at about 8 years in 2,839 mother-child pairs from the Avon Longitudinal Study of Parents and Children in the UK. Low maternal AA levels in pregnancy were linked to lower performance IQ, i.e. –2.0 points (95% CI –3.5 to –0.6; $p = 0.007$; increase in $R^2 = 0.27\%$), and low levels of DHA (22:6n-3) with a reduction of full scale IQ of –1.5 points (95% CI –2.9 to –0.1; $p = 0.031$; $R^2 = 0.15\%$). Kohlboeck et al. [38] reported a longitudinal cohort study with analysis of venous cord blood glycerophospholipid fatty acids at birth and behavior at age 10 years in 416 children in Munich, Germany. A 1% increase in DHA in cord blood serum decreased total behavioral difficulties by $(\exp)\beta_{\text{adj}} = 0.93$ (SE 0.02; $p = 0.0001$) and hyperactivity or inattentiveness by $(\exp)\beta_{\text{adj}} = 0.94$ (SE 0.03; $p = 0.04$). Higher LC-PUFA concentrations in cord blood serum were associated with fewer emotional symptoms [$(\exp)\beta_{\text{adj}} = 0.95$, SE 0.03; $p = 0.01$], and similarly higher AA concentrations were associated with fewer emotional symptoms [$(\exp)\beta_{\text{adj}} = 0.94$, SE 0.03; $p = 0.03$]. The results of these observational studies together suggest that the maternal AA and DHA status is relevant for fetal neural development and the long-term development of cognitive and emotional outcomes.

Two studies evaluated the impact of n-3 LC-PUFA supplementation during pregnancy and extended during the first 3 months postpartum on children's later cognitive development at 18 months [39] or at 7 years of age [40]. No beneficial effects of supplementation were found on mental development index (MDI) scores at 18 months or on cognitive scores on the Kaufman Assessment Battery for Children (KABC) test at 7 years.

LC-PUFA supplementation in breast-feeding women was reviewed in a Cochrane analysis [41]. A pooled analysis of outcomes in 5 clustered areas of neurodevelopment, i.e. language development, intelligence/problem-solving ability, psychomotor development, motor devel-

opment, and child attention, reported no significant overall effects in the rather heterogeneous studies, except for improved sustained attention at 5 years observed in a study supplementing breast-feeding women for 4 months with 200 mg DHA/day [42].

Since 2008, two studies have been published evaluating the impact of supplementation during breast-feeding. Jensen et al. [42] followed children of mothers who had been supplemented with 200 mg DHA/day during the first 4 months of lactation and at the children's age of 5 years observed higher scores on the sustained-attention subscale in the children of supplemented mothers. Previously reported findings from the same study [43] demonstrated a better performance of children of DHA-supplemented mothers on tests of psychomotor development at 30 months of age, which might be explained by improved sustained attention as documented at the older age. Another trial in breast-feeding Danish women [44] evaluated the impact of supplementation during the first 4 months of lactation on cognitive test scores at 7 years of age. That study found a faster speed of information processing in children of previously supplemented mothers, and lower scores for inhibitory control/working memory in children with a higher DHA status at 4 months.

Further evidence has emerged from analysis of the interaction of breast-feeding and genotype effects. Steer et al. [45] explored the interaction of postnatal breast-feeding and variation in the genotypes for *FADS* enzymes with regard to IQ scores assessed at about 8 years of age in 5,934 children born in the early 1990s in the UK. Breast-feeding was associated with higher IQ scores than bottle-feeding, which was not LC-PUFA supplemented or enriched at the time of the study. In children with a *FADS* genotype linked to a low endogenous LC-PUFA synthesis, breast-feeding supplying LC-PUFA provided an added benefit of more than 4 IQ points at school age compared to infants with a genotype supporting a more active LC-PUFA formation. Similarly, Morales et al. [46] found that Spanish children who had been previously bottle-fed formula without added LC-PUFA had an 8- to 9-point disadvantage in cognitive scores assessed at 14 months or at 4 years if there were homozygous for *FADS* genotypes linked to a low endogenous LC-PUFA synthesis compared to a genotype leading to more active LC-PUFA formation. Assuming that *FADS* genotypes are distributed at random in the population and are not related to the decision to breast-feed (the concept of 'mendelian randomization'), these data support a causal relationship between LC-PUFA supply during lactation and status in infancy and later cognitive achievements.

We conclude that the totality of recent RCT which are heterogeneous in outcomes and methods of assessment does not provide conclusive evidence of the benefits of added LC-PUFA supplementation during pregnancy and/or lactation for early cognitive or visual outcomes in offspring. However, the results of some high-quality randomized trials and observational as well as gene-nutrient interaction studies point to biologically important beneficial effects of an enhanced maternal pre- and postnatal LC-PUFA status on later attention, information processing, and cognitive performance.

The LC-PUFA content of human breast milk is not only derived from the current dietary intake [47], but a large proportion also comes from maternal body stores of LC-PUFA that have been previously deposited [48]. Therefore, it appears desirable to aim at securing an adequate maternal pre- and postnatal LC-PUFA status also to ensure an adequate LC-PUFA supply to the breast-fed infant to support child development.

Immune Response and Allergies

A systematic review that included 5 RCT on the effect of perinatal n-3 fatty acid supplementation on inflammatory markers and allergic diseases concluded that n-3 PUFA supplementation during pregnancy reduced the 12-month prevalence of positive egg skin prick tests and childhood asthma [49]. Since 2008, six studies have been published evaluating markers of immune response and/or allergic diseases in children of mothers supplemented with n-3 LC-PUFA or oily fish during pregnancy. All of these studies reported some positive findings on selected immune markers and/or the incidence of (allergic) diseases in the children of supplemented mothers. Supplementation with LC-PUFA or consumption of 2 portions of oily fish/week during pregnancy resulted in improvements in neonatal [50–53] and maternal [53, 54] immune responses, with attenuation of allergic inflammation, perhaps influenced by the infant allergic status.

Infants of supplemented mothers also showed lower rates of atopic eczema at 1 year of age [55, 56] and allergic asthma at 19 years of age [57]. A decreased occurrence of common colds and a shorter duration of common respiratory illnesses in the first 6 months of life were observed in infants of Mexican mothers supplemented with 400 mg algal DHA/day during pregnancy [58]. Four studies supplemented mothers during pregnancy and extended the supplementation during the first 3 or 4 months postpartum and reported positive effects on immune responses or allergic diseases. Furuhejm et al. [59] reported a lower prevalence of food allergy and a cumulative incidence of

immunoglobulin E (IgE)-associated diseases in the first 2 years of life after supplementing 145 at-risk pregnant women in Sweden with a provision of DHA and EPA during pregnancy and the first 3.5 months of breast-feeding [59]. Granot et al. [60] found changes in CD4 and CD8 cells compatible with attenuation of the proinflammatory response in the infants of 60 pregnant women supplemented with 400 mg DHA/day from early gestation until 4 months postpartum. A lower prevalence of atopic dermatitis (AD) was also observed in Finnish infants whose mothers had been supplemented with black currant seed oil during pregnancy until the cessation of breast-feeding, suggesting a possible beneficial role also for n-6 PUFA [61]. Follow-up of adolescents whose mothers had been randomized to supplementation with fish oil or olive oil capsules during pregnancy showed that fish oil provision in pregnancy markedly reduced the risk of asthma and particularly of allergic asthma at the age of 16 years [57].

Observational studies also reported a protective effect of fish intake in pregnancy and infancy on the allergic disease risk. Sausenthaler et al. [62] assessed 2,641 children and their mothers in a prospective birth cohort study in Germany (LISA). Higher maternal fish consumption (which provides n-3 LC-PUFA) during the last 4 weeks of pregnancy significantly reduced the risk of child eczema up to the age of 2 years (adjusted OR 0.75; 95% CI 0.57–0.98). Similarly, a higher fish consumption by pregnant women was linked to a lower allergic sensitization of their children in Italy [63], less doctor-diagnosed eczema in children in The Netherlands [64], and less eczema, allergic sensitization, and atopic wheezing in Mexican children [65].

Recently, Standl et al. [66] reported a marked breast-feeding-gene interaction effect on doctor-diagnosed asthma up to the age of 10 years. In children with an *FADS* genotype resulting in low LC-PUFA synthesis, longer breast-feeding, which would support an improved LC-PUFA status in infancy, reduced the asthma risk by 57–61%, whereas there was no significant effect of breast-feeding in children homozygous for the major genetic allele [66]. These studies lend further support to the conclusion that the LC-PUFA status in early life is very important for long-term protection against childhood allergies.

With respect to the infants' anti-infectious response, increased IgG titers to common childhood vaccines were found in infants after LC-PUFA supplementation during pregnancy [59]. Moreover, daily supplementation of 400 mg DHA from algal oil compared to placebo from 18–22 weeks of gestation to birth in a double-blind RCT in

Mexican pregnant women showed in infants ($n = 834$) beneficial effects of maternal DHA supplementation on a reduced rate of respiratory tract infections at the age of 1 month (RR 0.76; 95% CI 0.58–1.00) and on the infant disease burden at the ages of 1, 3, and 6 months [58]. For example, at the age of 6 months, the duration of fever was reduced by 20%, nasal secretions by 13%, dyspnea by 54%, skin rashes by 23%, and other symptoms by 25%. These effects might be mediated by modulation of DNA methylation and Th1/Th2 balance [67].

In summary, current evidence suggests a beneficial effect of oily fish intake or supplementation with fish oils or with DHA-rich algal oil during pregnancy on immune responses involved in allergic inflammation, on the incidence of allergic conditions, and on anti-infectious protection and the infection disease risk in children.

Maternal Depression

One systematic review included 10 articles (cohort studies, RCT, and pilot trials) that evaluated the impact of maternal n-3 fatty acid supplementation on perinatal maternal depression. Inconsistent results were observed, with 6 studies finding no association, 2 showing mixed results, and 2 reporting a positive association between n-3 PUFA and a reduced incidence of maternal perinatal depression [68]. The authors concluded that the heterogeneity of the results could be explained by the heterogeneity of the studies, with different study durations and time periods and other differences in PUFA interventions.

Four studies evaluated maternal depression outcomes after supplementation with n-3 LC-PUFA during pregnancy and lactation. Three of those studies [24, 69, 70] did not observe differences in maternal depressive symptoms after supplementation. A small study in 36 pregnant women in China with diagnosed major depressive disorders found significantly lower depression scores after an 8-week daily supplementation during pregnancy with 3.4 g n-3 PUFA [16].

In summary, evidence for the role of maternal n-3 LC-PUFA supplementation in perinatal depression is inconclusive. More research is needed to confirm or refute the observation that mothers with more severe risks of depression may benefit from supplementation.

Growth, Obesity, and Early Markers of Cardiovascular Disease and Oxidative Stress

Maternal supplementation with 400 mg/day DHA from algal oil during pregnancy in Mexico increased infants' length at 18 months of age, but only in firstborn

children [34]. No impact of cod liver oil supplementation during pregnancy and the first 3 months after delivery was found on children's height, weight, or BMI at 7 years of age [40]. Maternal AA and n-6 LC-PUFA concentrations during gestation and lactation were negatively related to the BMI and the ponderal index at 1 year of age [21], but no differences in abdominal fat mass or fat distribution were observed in infants of German mothers supplemented with 1,200 mg n-3 LC-PUFA from the 15th week gestation until 4 months postpartum [71].

Three systematic reviews evaluated the impact of maternal n-3 fatty acid supplementation on children's later body composition or body weight. The reviews included studies that supplemented mothers during pregnancy, lactation, or both. Inverse associations between maternal n-3 LC-PUFA intake or supplementation and the children's later body composition (adiposity, BMI, or body weight) were observed in some but not all studies [72–74]. A recent review including 6 controlled trials of pre- or postnatal n-3 LC-PUFA supplementation concluded that currently there is little evidence to support the hypothesis that LC-PUFA supplementation during pregnancy and lactation prevents childhood obesity [75].

Two controlled studies evaluated markers of early cardiovascular disease (CVD) at 7 and 19 years of age, respectively, in children whose mothers had been supplemented with fish oil or placebo during pregnancy [76–79]. No differences in adiposity, plasma lipids, plasma lipoproteins, blood pressure, heart rate, or heart rate variability were reported in Danish children aged 19 years whose mothers had been randomized to receiving daily fish oil, olive oil, or no oil during pregnancy. Adverse effects on blood pressure, energy intake, and physical activity at 7 years of age were observed in boys, but not in girls, after fish oil supplementation during the first 4 months of lactation [76]. In contrast, lower umbilical cord blood insulin concentrations were observed in infants of mothers who had been supplemented with cereal-based DHA-fortified food during pregnancy, but that study was small and suffered from methodological flaws [23].

Two studies evaluated markers of oxidative stress and did not report any differences between pregnant mothers supplemented with LC-PUFA or oily fish and nonsupplemented mothers [80, 81].

In summary, the current evidence for a possible programming effect of maternal n-3 fatty acid supplementation on child growth, obesity risk, and early markers of CVD is limited and does not allow firm conclusions.

LC-PUFA Supply to Infants Born at Full Term

A total of 14 original studies that evaluated the impact of n-3 LC-PUFA supplementation during infancy in term infants were included. In addition, we evaluated 6 systematic reviews and meta-analyses that reported findings in term infants.

Cognitive Development

All meta-analyses in this area are limited by a large degree of heterogeneity between the included studies, in particular regarding interventions, dosages, selected outcomes, and methods of outcome assessment. Moreover, the available intervention trials did not adjust for genetic variation in PUFA metabolism (*FADS* genotypes). A meta-analysis of 15 randomized studies on the effects of LC-PUFA supplementation in term infants did not show significant beneficial effects of supplementation on either mental or psychomotor development [82]. This finding was repeated in another meta-analysis including 12 trials involving 1,802 infants and demonstrating no significant effect of LC-PUFA supplementation of formula on early infant visual development and cognition [83, 84]. Outcomes regarding visual acuity were inconsistent: no overall benefits were reported in a Cochrane review, with 5 out of 9 studies not showing a beneficial effect [82]. In contrast, a meta-analysis involving 1,949 infants from 19 studies found a significant benefit for infants' visual acuity after LC-PUFA supplementation up to 12 months of age [83]. Studies that provided higher doses of DHA (at least 0.32% in formula) and AA (at least 0.65% in formula) for a longer duration (>1 year) and measured visual acuity with electrophysiological tests were more likely to show beneficial effects of supplementation in term infants [82].

Nine studies have been published since 2008 evaluating the impact of LC-PUFA supplementation in term infants on several aspects of cognitive development. Two of these studies [85, 86] have already been included in the 3 meta-analyses [82–84].

Studies have evaluated mental development, visual acuity, or motor development during infancy or in young childhood and the results have been mixed: one study providing high-dose fish oil with n-3 LC-PUFA but without AA did not observe beneficial effects on Bayley Scale of Infant Development (BSID) scores [87], one observed a beneficial effect on the mental development index [85], and another study reported beneficial effects on visual acuity [86] when 3 different DHA dosage groups were combined. These data may indicate that effects at younger ages may be too subtle to detect with smaller sample

sizes. Supplementation with LC-PUFA in term infants shortened the time to achieving a milestone of motor development (sitting without support) [88].

Four studies assessed cognitive development at school age when the children were 6 or 9 years of age. Two of these studies [89, 90] reported beneficial effects on various aspects of cognition (attention, fine-grained tasks, speed of processing, and problem solving), suggesting that the effects of LC-PUFA supplementation in early life may be better detectable at a later age in more specific or fine-grained tasks. The other 2 studies, however, reported no beneficial effects on selected outcomes in LC-PUFA-supplemented children [91, 92].

In summary, among the recently published studies, some studies supplementing formula for term infants with LC-PUFA found benefits with regard to visual, motor, and cognitive outcomes in early childhood, and even more pronounced benefits in later childhood. However, other studies found no significant beneficial effects. There was no evidence of untoward effects. There is a trend toward a greater likelihood of benefit with higher dosages (DHA $\geq 0.32\%$ and AA $\geq 0.66\%$) and a longer duration of a higher postnatal LC-PUFA supplementation (up to 1 year of age). As discussed before, further evidence for the benefits of a postnatal LC-PUFA supply is derived from gene-nutrition interaction studies that report greater benefits of breast-feeding, which provides preformed LC-PUFA, in infants genetically determined to have a lower endogenous LC-PUFA synthesis [45, 46].

Growth/Anthropometry

A systematic review of 13 studies in term infants found no effects of LC-PUFA supplementation on growth [82]. Rosenfeld et al. [93] performed a meta-analysis based on individual patient data of 901 children from 4 RCT of formula milk with and without LC-PUFA and found no evidence that supplementation affects children's growth at 18 months of age. A previous meta-analysis including 14 trials with 1,846 infants showed no significant effect of LC-PUFA supplementation with infant formula on infant weight, length, or head circumference at any assessment age [94]. Of interest, that meta-analysis reported that supplementation of infant formulae with n-3 LC-PUFA but no AA showed a mean reduction in plasma AA of 25% relative to the control groups [94]. The potential biological relevance of these reduced AA levels is uncertain.

Since 2008, five studies with LC-PUFA supplementation in term infants have reported effects on growth and/or the evolution of the BMI during infancy [95–98] or at 9 years of age [99]. None of these studies observed differ-

ences in anthropometric measurements between supplemented and nonsupplemented infants, and there was no effect of fish-oil supplementation on growth hormone IGF-1 production in a study in Denmark [98].

In summary, the available studies published to date do not provide evidence that LC-PUFA supplied to term infants would change infant or later childhood growth or obesity risk.

Allergies and the Immune Response

Studies evaluating the effect of LC-PUFA as well as other nutrient interventions on AD in children were recently reviewed [100]. The authors concluded that γ -linolenic acid supplementation in healthy infants seems to reduce the severity of AD. Supplementation with prebiotics and black currant seed oil (γ -linolenic acid and n-3 fatty acids) was effective in reducing the development of AD.

We found 4 studies published since 2008 that evaluated the impact of LC-PUFA supplementation in term infants on immune markers and/or allergies. Three of these studies found beneficial effects of supplementation on immune markers [101, 102] or allergic diseases [103]. D'Vaz et al. [102] randomized 420 term infants with a high risk of allergy to a daily supplement of fish oil (280 mg DHA, 100 mg EPA) or placebo from birth until 6 months of age. They found lower allergen-specific Th2 responses and elevated Th1 responses in the fish oil group, suggesting a potentially allergy-protective effect on immune function [102]. Improved immune parameter responses after LC-PUFA supplementation were also observed in formula-fed term infants at 16 weeks of age [101]. In contrast, no differences in responses to childhood vaccines were observed after n-3 LC-PUFA and AA supplementation in 12-month-old formula-fed term infants in Australia [97].

Term infants receiving different dosages of DHA (0.32–0.36% fatty acids) and AA (0.64–0.72%) from 1–9 days of life until 12 months of age had lower odds of developing lower respiratory tract infections, wheezing/asthma, or other allergic diseases than controls, regardless of the dosage of DHA received [103]. No differences in childhood allergic diseases were observed in infants with a high atopy risk at 6 months of age, despite the fact that immune parameters had been altered [104], suggesting that longer follow-up times may be required before effects on disease become apparent.

Protective effects of fish intake with complementary feeding in infancy on allergic conditions were found in 2 large prospective birth cohort studies in Scandinavia. In

a study in 4,921 infants, introduction of fish prior to the infant age of 9 months reduced the eczema risk at 1 year (RR 0.76; 95% CI 0.62–0.94; $p = 0.009$) [105]. In 4,089 children followed from birth, provision of more than 2–3 portions of fish per month in infancy compared to less the 2 portions per month at the age of 4 years led to a significantly reduced risk of asthma (RR 0.68; 95% CI 0.51–0.92), eczema (RR 0.69; 95% CI 0.57–0.84), allergic rhinitis (RR 0.57; 95% CI 0.45–0.73), any allergic disease (RR 0.65; 95% CI 0.54–0.77), and allergic sensitization (RR 0.66; 95% CI 0.53–0.82) [106].

Further support for the conclusion that the LC-PUFA status in infancy impacts the allergic disease risk stems from the observation of marked protective effects of breast-feeding for at least 3 months, which reduces the risk of physician-diagnosed asthma at up to 10 years of age in subgroups defined by LC-PUFA metabolism. Breast-feeding with the provision of LC-PUFA reduced the asthma risk up to 10 years of age by about one half in children who had an *FADS* genotype determining a low LC-PUFA synthesis.

In summary, fish intake and an enhanced LC-PUFA status in infancy appear to have a protective effect on the development of allergic diseases in childhood.

Other Outcomes

de Jong et al. [91] measured the CVD risk at 9 years of age in term infants who had been supplemented with LC-PUFA formula ($n = 146$; 0.45% AA and 0.30% DHA) or standard formula ($n = 169$) during the first 2 months of life. No differences in blood pressure or heart rate were observed between the 2 intervention groups.

In a study in Thailand, 144 healthy term infants were supplemented with whey-based formula containing LC-PUFA and oligosaccharides or placebo formula from 30 days to 4 months of life [95]. Beneficial effects on gastrointestinal comfort (gastric transit time, intestinal transit time, hard stools, and stool microbiota) were reported.

Colombo et al. [107] randomized 133 infants born at term to receive for the first year of life formula either with no LC-PUFA or with DHA at levels of 0.32, 0.64, or 0.96% fatty acids combined with 0.64% AA. All LC-PUFA-enriched formula groups showed a reduced heart rate, without a recognizable dose-response relationship to levels of DHA intake [107]. These results confirm previous observations by Pivik et al. [108] who reported higher heart rates and lower values for heart rate variability measures in infants fed diets without DHA compared to DHA-containing formula. The effects appeared

from 4 months onwards and were interpreted as increased parasympathetic tone in infants receiving DHA. In adults, a decreased heart rate is considered a positive health outcome.

Older Infants

Five studies published since 2008 have assessed the effect of LC-PUFA supplementation in older infants (aged >3 months) and young children. One of these studies was performed in a disadvantaged population of infants from a low-income country [109]. Overall, very few positive effects of LC-PUFA supplementation in older infants and young children have been reported since 2008. In Gambia, LC-PUFA supplementation in healthy infants from 3 to 9 months of age increased the mid-upper-arm circumference and skinfold thickness at 12 months of age [109], whereas no growth effect was observed in Danish infants supplemented with fish oil from 9 to 18 months of age [110]. No effects on morbidity or gut integrity were found in the Gambia study [109]. Fish oil supplementation modified the fecal microflora in a subgroup of infants from the Danish study who had been weaned prior to the onset of supplementation [111].

A study in Australian children randomized to active diet interventions to increase $n-3$ and decrease $n-6$ intakes from weaning until 5 years of age or controls and did not find changes in blood pressure or arterial structure at 8 years of age [112].

Observations in infants who had been supplemented with fish oil from 9 to 12 months of age showed a 6% longer mean RR interval in fish-oil-supplemented boys ($p = 0.007$). Irrespectively of gender, there was an association between RR interval changes and erythrocyte $n-3$ PUFA ($p < 0.001$), suggesting a beneficial effect of fish oil supplementation in older infants on early markers of CVD risk [113]. Fish oil supplementation also induced beneficial effects on free-play scores and looking behavior and decreased the systolic blood pressure [114].

Evidence in Preterm Infants

We evaluated data from 3 trials in preterm infants that published results since 2008. Most studies in preterm infants evaluated the effects of DHA supplies with human milk or formula near a 0.2–0.3% fat content. This amount is considered insufficient to support the average daily whole-body DHA accretion in excess of 50 mg/kg of body

weight that occurs in utero, which requires a DHA supply of about 1% human milk or formula fat [115]. In a large RCT, Makrides et al. [115] randomized 657 preterm infants to a conventional (0.3%) or higher (1%) DHA supply, along with about 0.6% AA, from day 2 to day 4 of life until a term-corrected age. The findings of that trial were reported in a number of different publications [116–119]. In addition, one meta-analysis specifically reported on the effects of LC-PUFA supplementation in preterm infants [120].

Cognitive Development

Four out of 7 studies included in the meta-analysis [120] did not show a beneficial effect of supplementation on cognitive outcomes evaluated at 12 or 18 months of age. The 3 trials that showed beneficial effects on cognitive development all used the newer version of the BSID, suggesting that other methods might not have been sensitive or precise enough to detect effects. No beneficial effects of LC-PUFA supplementation on visual acuity were seen in the 16 studies included in the meta-analysis that evaluated visual acuity [120].

Two of the 3 studies that reported outcomes on child neurodevelopment showed no beneficial effects of LC-PUFA supplementation in preterm infants on cognitive outcomes at an early age [18 months; school age (language)] or behavior at 3 or 5 years of age (general cognitive tests at 10 years of age) [115, 121, 122]. However, beneficial effects of supplementation were observed in certain subgroups. For instance, girls provided a high DHA intake (1%) along with AA had higher MDI scores at 18 months of age [115]. In the total population, the occurrence of significant mental delay (mental developmental index <70) at 18 months was markedly reduced by one half ($p = 0.03$), which is considered a major benefit for the developmental outcome.

Another study in children aged 10 years found higher language scores in children who previously as preterm infants had been randomized to a DHA-containing formula compared to controls who did not get DHA in early life [122]. In addition, children who received DHA formula and no breast milk had better IQ and memory scores at 10 years of age, whereas this effect was not apparent in those who received formula with breast milk (which provides DHA) [122]. Beneficial effects of supplementation on recognition and problem solving at 6 months of age were also observed in a group of very preterm infants (birth weight <1,500 g) who had been supplemented with DHA and AA in the first 9 weeks of life [123]. Better visual acuity at 4 months' corrected age was observed after

DHA-supplemented formula in Australian preterm infants [124].

In summary, while there is considerable heterogeneity among the available studies, there are consistent indications that an LC-PUFA supply to preterm infants can have benefits for visual and cognitive outcomes, with evidence from one large high-quality trial indicating DHA dose dependency. Certain subgroups of preterm infants, e.g. with a lower birth weight, may achieve a greater benefit from a preformed LC-PUFA supply.

Growth/Anthropometry

Preterm infants fed with high-DHA formula during early infancy in the Australia DINO trial were 0.7 cm longer at 18 months of age, and those born with a higher birth weight ($\geq 1,250$ g) also had an increased later weight [118]. Higher body weights at 10 years of age in girls, but not in boys, were also observed in children who had been born preterm and had received LC-PUFA-supplemented formula until 9 months of age [122]. However, these results were not confirmed by a meta-analysis, which did not find effects of providing LC-PUFA to preterm infants on weight, length, or head circumference at 12 months (4 studies) or 18 months (2 studies) in spite of an increased weight and length at 2 months postterm in supplemented infants [120].

In summary, there are conflicting data on the effects of LC-PUFA supply to preterm infants on postnatal growth, with some data indicating potential benefits for length growth in early childhood.

Other Outcomes in Preterm Infants

A reduced incidence of reported hay fever at 12 and 18 months of age and a reduction in chronic lung disease in boys and in infants born with a birth weight <1,250 g were observed in preterm infants randomized to a higher DHA supply (1%) along with AA as compared to a lower DHA supply (0.3%) in the previously cited study by Makrides and coworkers [117]. An earlier study in preterm infants demonstrated comparable lymphocyte populations, cytokine production, and antigen maturity between infants receiving LC-PUFA-supplemented formula and those receiving human milk, whereas infants receiving an unsupplemented formula differed in these immune parameters [101, 125].

Follow-up of a subgroup of previously preterm born children at the age of 10 years did not show differences in growth or blood pressure, whereas a subgroup analysis among girls who had received formula with added DHA but no AA postnatally had a slightly higher blood pres-

sure, but there were no significant differences after adjustment for current body weight [126].

In summary, the reported positive effects of early LC-PUFA supplementation in preterm infants on chronic lung disease and the immune response are promising and should prompt further investigation.

Recent Recommendations on Pre- and Postnatal LC-PUFA Supply

Previously, scientific experts and learned societies recommended that pregnant and lactating women should achieve an average daily intake of at least 200 mg DHA, which can be reached by eating 2 portions of fish per week if this includes oily fish [11, 12, 127, 128]. Alternatively, the use of supplements has been recommended for women that do not achieve this level of fish consumption. There is a broad consensus that breast-feeding, which provides preformed LC-PUFA, is the optimal choice for infant feeding [129]. It was also concluded that formulae for term infants should contain DHA at levels between 0.2 and 0.5 weight percent of total fat, with the minimum amount of AA at least equivalent to the content of DHA. The dietary LC-PUFA supply should continue after the first 6 months of life, but no quantitative recommendations were provided since there was not sufficient information at that time.

The European Food Safety Authority (EFSA) determined adequate intakes per day of 250 mg for EPA plus DHA for adults based on cardiovascular considerations and an added 100–200 mg preformed DHA during pregnancy and lactation to compensate for oxidative losses of maternal dietary DHA and accumulation of DHA in the body fat of the fetus/infant [130]. In the year 2010, the EFSA further recommended a DHA intake of approximately 20–50 mg/day for young infants aged 0–6 months and an intake of 100 mg DHA at 6–24 months to support optimal growth and development. More recently, in 2013, the EFSA considered the following nutrient intakes adequate for the majority of infants and young children: 100 mg DHA/day and 140 mg AA/day from birth to age <6 months, 100 mg DHA/day from 6 to <24 months, and 250 mg EPA + DHA/day after the age of 24 months [131]. Recently, the EFSA shared a draft opinion on the compositional requirements of infant and follow-on formulae and advised that both infant and follow-on formulae should contain 20–50 mg DHA/100 kcal (at an assumed mean fat content of 5.2 g/100 kcal, ~0.38–0.96% of fat), while it was not consid-

ered necessary to set a minimum requirement for AA content [132]. However, this panel notes that no adequate clinical studies have evaluated the suitability and safety of feeding infant formula from birth with DHA contents of up to about 1% fat and no content of AA. Therefore, the EFSA proposal is not supported by this panel.

In 2010, the Food and Agriculture Organization of the United Nations (FAO) concluded that for pregnant and lactating females the minimum intake for optimal adult health and fetal and infant development is 0.3 g/day EPA + DHA, of which at least 0.2 g/day should be DHA [133]. For infants aged 0–6 months, the FAO recommended a DHA intake of 0.1–0.18% of energy intake and an AA intake of 0.2–0.3% of energy intake based on human-milk composition. For infants above the age of 6 months, a DHA supply of 10–12 mg/kg/day was recommended without specifying a requirement for AA [133].

Recent recommendations for the compositional requirements of follow-up formula suitable for feeding from the age of about 6 months onwards stipulate an optional DHA content of up to 1% fatty acids, while the evidence available was considered insufficient to set a minimal quantitative requirement for added AA in follow-up formula that provides DHA [134]. This was based on the consideration that the ability to maintain AA stores from endogenous synthesis increases during the second half of the first year of life [135], and that dietary preformed AA is usually provided by a variety of complementary foods during the second half of the first year of life.

For preterm infants, daily intakes of 12–30 mg DHA and 18–42 mg AA per kilogram of bodyweight or 11–27 mg DHA/100 kcal of energy intake and 16–39 mg AA/100 kcal were recommended by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) in 2009 [136], though these recommendations were developed before the full information on the trial in preterm infants evaluating the suitability and safety of higher dosages [117, 118, 137] had become available. It was also recommended that the ratio of AA to DHA should be in the range of 1.0–2.0 to 1 (wt/wt), and the EPA (20:5n-3) supply should not exceed 30% of the DHA supply [136]. A recent international expert group with contributors from all 5 continents reviewed the nutritional needs of very-low-birth weight infants (birth weight <1,500 g). They concluded that very-low-birth weight infants should receive per kilogram and per day between 385 and 1,540 mg linoleic acid and >55 mg α -linolenic

acid. Intakes of DHA ranging from 18 to 60 mg and intakes of AA ranging from 18 to 45 mg were considered reasonable, while EPA intakes should not exceed 20 mg; however, DHA intakes of 55–60 mg, along with AA intakes of 35–45 mg, were considered preferable (all per kg and per day) [138].

LC-PUFA Supply in Asian Populations

Many populations in Asia have traditionally regularly consumed fish and seafood, and hence they have had a relatively high intake of preformed EPA and DHA. However, in recent years the fish intake has tended to markedly decrease while the meat consumption has increased, with a resulting decreased intake of DHA and EPA and an increase in AA intake (fig. 1), particularly among younger women (fig. 2), as documented in the Japanese National Health and Nutrition Survey [139] and in the Korean National Health and Nutrition Examination Survey [140, 141]. Vegetarian and vegan diets are commonly followed not only in India but also in other Asian countries and have recently gained popularity particularly among young women of childbearing age [142–145]. Vegetarian diets provide very little, and vegan diets provide basically no, preformed LC-PUFA. DHA supplementation is advisable, and vegetarian sources of DHA from algal oils are available.

A recent review evaluated the essential fatty acid intakes and status of pregnant and lactating women, infants, and children in developing countries and reported on findings from Asian countries [146].

In pregnant women, the lowest DHA intakes were reported in India in the third trimester of pregnancy at only 11 mg [27], and in Bangladesh the DHA intake was only 30 mg/day [147].

The mean concentration of DHA in breast milk is quite variable in Asian countries where there is data available. Some countries have reported lower levels of DHA in breast milk, e.g. 0.23% in Nepal [148], and 0.30% in Bangladesh [147], whereas higher DHA levels than the approximately 0.3% typically found in breast milk in Western countries [149] were reported in the Philippines ($0.74 \pm 0.05\%$) and a coastal area of Southeastern China ($0.61 \pm 0.46\%$) [150] and about 1% was reported in Japan [151]. These data reflect that the DHA content in human milk directly responds to the maternal dietary DHA intake [47].

Very few studies have reported intake or status data of infants from Asian countries, and intakes vary signifi-

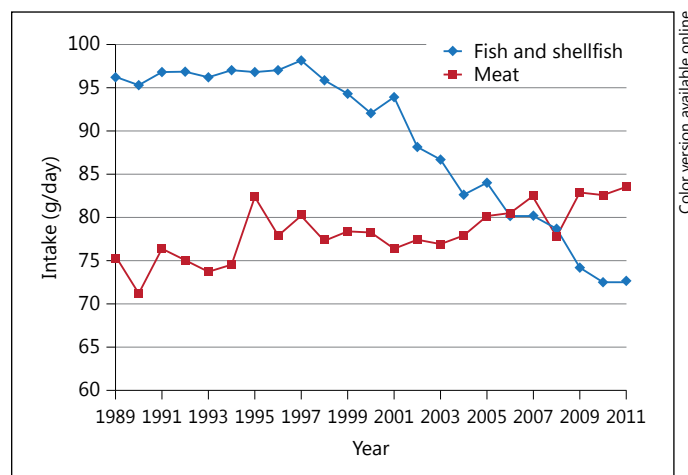


Fig. 1. A marked decrease in the average consumption of fish and shellfish, along with an increase in meat intake, occurred in Japan during a period of about 20 years and resulted in a marked decrease in the dietary supply of DHA as well as in the dietary DHA-to-AA ratio. Drawn from data of the Ministry of Health, Labour, and Welfare, Japanese Government [139].

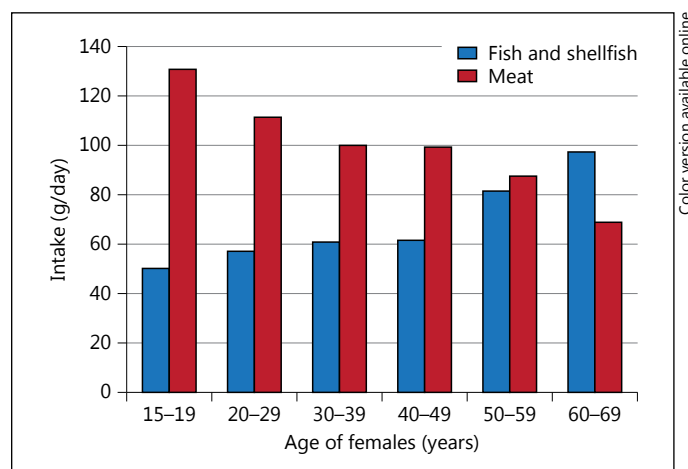


Fig. 2. The intake of meat is particularly high and that of fish and shellfish is particularly low among younger women of childbearing age in Japan. Drawn from data of the Ministry of Health, Labour, and Welfare, Japanese Government [139].

cantly across the region and within countries. In Bangladesh, the total fat intakes were extremely low at 19.5% of energy in breast-fed children and only 12.7% of energy in non-breast-fed children at 24–35 months of age [147], whereas in children aged 1–3 years in rural areas from the Yunnan Province in China the mean fat intake was $24 \pm 7\%$ of energy [152].

Only 2 studies reported status data of infants and children from Asian countries. Low DHA levels in RBC were reported in Pakistani infants, corresponding to a low DHA content in maternal milk [153]. In an intervention study, the baseline fatty acids statuses of 6-month-old Cambodian and Italian infants were compared. Cambodian infants had lower baseline levels of LA, comparable ALA levels, and higher levels of AA + EPA + DHA in blood compared to their Italian counterparts [154]. Subsequent multiple micronutrient supplementation in those Cambodian infants resulted in significantly higher levels of DHA at 18 months of age compared to infants in the other intervention groups who received only iron-folic acid or placebo, respectively.

Conclusions and Recommendations

This review revealed a general scarcity of data on n-3 LC-PUFA supply and benefits in Asian populations. Future research should include this region, acknowledging its large variety of people and dietary habits. With many countries experiencing a rapid nutritional transition, future research should include indicators of chronic diseases such as gestational diabetes and programming effects on future CVD risk factors.

Since the responses to supplementation are likely to depend on current intakes and on nutritional status, future research evaluating the benefits of LC-PUFA supplementation should control for baseline nutritional status and intakes, as well as genetic variation, e.g. in the *FADS* genotype. Studies evaluating child development should use task-specific, sensitive tests focusing on areas likely to benefit from DHA and AA supplementation, including, for example, sustained attention and memory recognition.

Recent evidence indicates that n-3 LC-PUFA supplementation during pregnancy reduces the risk of early preterm birth prior to 34 weeks of gestation, which would predict a major benefit for infant morbidity and mortality. It is recommended that pregnant women should aim to achieve an added minimum average daily supply of 200 mg DHA over and above the intake level recommended for adult general health, resulting in a total DHA intake of at least 300 mg/day. Based on the comparison of studies with different dosages, it seems possible that higher intakes (600–800 mg DHA/day) may provide greater protection than lower dosages, but direct comparative dose-effect evaluations are not available.

Some but not all studies evaluating the effects of DHA or EPA + DHA supplementation in pregnant and lactating women and in term infants indicate possible beneficial effects on later child visual and cognitive and emotional development. The LC-PUFA supply and fish intake in pregnancy and infancy seem to positively affect the development of immune responses involved in allergic reactions, and reduce the risk of allergic diseases (asthma and eczema). Further support for the beneficial effects of early LC-PUFA status on later cognition and asthma risk is provided by recent diet-gene interaction studies.

Breast-feeding is recommended as the preferred choice for infant feeding. Breast-feeding women should aim to achieve a minimum average daily supply of 200 mg DHA, which is expected to result in a milk DHA content of 0.3% of fatty acids [47]. During the first months of life, term infants should receive 100 mg DHA/day and 140 mg AA/day, and hence infant formula should provide at least 0.3% of fatty acids as DHA along with AA. We recommend a continued supply of 100 mg DHA/day during the second 6 months of life. We do not provide quantitative advice on AA intake with follow-on formula fed once complimentary foods have been introduced due to a lack of sufficient data and due to considerable variation in the amounts of AA provided by complimentary foods within and among countries.

There are indications of benefits of supplying DHA in combination with AA to preterm infants with respect to cognitive and visual development and in infants with a birth weight <1,250 g with respect to the prevention of neurodevelopmental handicaps and chronic lung disease, with apparent greater benefits provided by a higher compared to a lower DHA supply (1 vs. 0.35% of the total fatty acid intake). For very-low-birth weight infants (birth weight <1,500 g), we support the recent recommendations [138] that intakes per kilogram per day of DHA ranging from 18 to 60 mg and of AA ranging from 18 to 45 mg are reasonable, and EPA intakes should not exceed 20 mg EPA; while intakes per kg per day of 55 to 60 mg DHA (~1% of the total fatty acid intake), along with 35–45 mg AA (~0.6–0.75% of the total fatty acid intake) are considered preferable.

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