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Docosahexaenoic Acid and Arachidonic Acid Nutrition in Early Development

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INTRODUCTION

Docosahexaenoic acid (DHA; 22:6–3) is an omega-3 fatty acid with 22 carbons and 6 double bonds (22:6n-3). Arachidonic acid (ARA; 20:4–6) is an omega-6 fatty acid with 20 carbons and 4 double bonds. These two fatty acids are the predominant long-chain (20 and 22 carbons) polyunsaturated fatty acids (LCPUFAs) in human brain [1,2]. Brain DHA begins to accumulate around 22 weeks' gestation and the absolute amount per gram of brain as well as the weight percent of total fatty acids increases progressively from 22 weeks until at least 2 years of age [3–6]. The absolute amount of ARA per gram of brain also increases in brain but decreases in weight percent of total fatty acids after birth [1].

All human milk contains ARA and DHA to support DHA and ARA requirements for the growing and developing brain as well as other organs and tissue after birth. In human milk, the amount of ARA typically exceeds that of DHA. Milk ARA content is also less varied than DHA and, unlike DHA, does not seem to be linked to maternal intake. Because worldwide DHA intake is variable, milk DHA content is variable across cultures. Reports of milk DHA concentration range from 0.05% of total fatty acids in vegan vegetarians [7] to 2.8% in the marine region of China, where a diet high in seafood is consumed [8]; the median value of DHA in human milk worldwide is ~0.3% [9]. Women in the United States have low milk DHA levels (levels around 0.1% DHA are typical [10]) unless they regularly consume DHA or a supplement during and/or after their pregnancy. Jensen and colleagues [11] found that a supplement of 200 mg of DHA per day in US women could increase milk

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DHA to ~0.3% of total fatty acids, which is the amount that the European Food Safety Authority (EFSA) requires in infant formula in order to make a claim for support of infant visual development [12].

Red blood cell DHA and ARA levels are lower in infants fed formula without DHA and ARA, compared with infants fed human milk [10,13,14]; this is evidence of lower status. However, autopsy studies find lower brain DHA levels and higher omega-6 LCPUFA levels in infants fed formula without LCPUFA [14–16]. In term infants, frontal cortex DHA level is about 20% [14] lower if fed formulas without DHA and ARA. In preterm infants, who do not have the same opportunity to accumulate DHA from placental transfer, the amount of DHA that accumulates is ~50% less if formula is lacking in DHA and ARA [15].

DHA, ARA, and docosatetraenoic acid (DTA; 22:4–6) are the major LCPUFAs in brain phosphoglycerides [6,14,15,17]; however, the amount of omega-6 LCPUFAs (ARA, DTA, and docosapentaenoic acid [omega 6 DPA; 22:5–6]) exceeds the amount of DHA in the brains of humans and nonhuman primates. It is not known what happens to brain composition if human infants are fed only omega-3 LCPUFA (DHA or DHA plus EPA); however, some studies suggest that diets feeding only omega-3 result in major reductions in the omega-6 to omega-3 LCPUFA ratio. Baboon infants fed a formula with a higher proportion of DHA than ARA (0.96% and 0.64%, respectively) were shown to have reduced cortical and hypothalamic omega-6 LCPUFA levels, and omega-3 LCPUFA level exceeded that of omega-6 LCPUFA in the frontal lobe [18]. A recent trial conducted in our laboratory (the DHA Intake and Measurement of Neural Development [DIAMOND] trial, discussed later) included a formula in which omega-3 LCPUFA intake was substantially higher than omega-6 LCPUFA intake, and in which outcomes were somewhat consistent with these animal studies.

It seems advisable and prudent to follow human milk as a model for adding LCPUFA in infant formula given that the optimal balance of these two families of fatty acids in the developing brain is unknown. Infant formulas in the United States have contained both DHA and ARA since 2002, typically in a ratio of ~2:1 of ARA to DHA, although the amounts of DHA and ARA fed vary. Before 2002, all formula-fed preterm and term infants in the United States received formula without DHA and ARA.

Long-chain polyunsaturated fatty acid intake as a source of docosahexaenoic acid and arachidonic acid

As noted previously, human newborns obtain both DHA and ARA from human milk and infant formulas currently contain these fatty acids. However, other foods provide little DHA and ARA in the diet of US infants. Using validated assessments of food intake in 207 infants, the authors estimated DHA intake at 9 and 12 months of age to be on average 4.0 mg (median = 0 mg) and 13 mg (median = 4 mg), respectively. ARA intake from foods other than human milk or formula in the same 207 infants at the same ages was estimated respectively to average 15 mg (median = 4 mg) and 41 mg (median = 20 mg) at 9 and 12 months of age. Fish, chicken, and egg yolk are good food sources of DHA and ARA, but only 3 of 207 children were reported to have consumed these foods on the day of their 12-month, 24-hour dietary recall (Carlson SE, unpublished data, 2016). US infants may depend

on human milk or formulas with DHA and ARA for their primary intake of these nutrients in infancy. After infancy, DHA intake in US children is not appreciably higher than is found at 12 months of age [19].

Fetal stores as a source of docosahexaenoic acid

Evidence suggests that DHA accumulated in fetal adipose tissue can support DHA requirements for some time after birth [20]. Beginning around 26 weeks' gestation, DHA accumulation increases progressively in fetal adipose tissue to term birth. However, the amount accumulated depends on maternal DHA intake. Haggarty [20] suggests that there is little to no accumulation of DHA in fetal adipose tissue if maternal intake is less than 90 mg/d; this is significant because the mean reported intake of DHA from food and supplements of US women 19 to 50 years of age is only 53 mg/d [21]. The offspring of US women may accumulate less adipose DHA than the offspring of women in populations with much higher DHA intake.

Long-chain polyunsaturated fatty acid synthesis as a source of docosahexaenoic acid and arachidonic acid

All omega-6 and omega-3 LCPUFAs (including DHA and ARA) can be obtained by synthesis from their 18-carbon precursors. DHA can be synthesized from alpha-linolenic acid (18:3–3) and ARA can be synthesized from linoleic acid (18:2–6) through a process of elongation and desaturation. However, none of the many studies to date has found equivalent DHA and ARA status in developing infants fed 18-carbon fatty acids compared with infants fed LCPUFAs, and this is particularly true for DHA. Conversion of alpha-linolenic acid to EPA and DHA is decreased by high dietary intake of linoleic acid, because linoleic acid (an omega-6 fatty acid) competes with alpha-linolenic acid (an omega-3 fatty acid) for the same elongation and desaturation pathway [22]. High linoleic acid intakes and a high ratio of linoleic acid to alpha-linolenic acid are characteristics of most persons in the United States; linoleic acid has increased dramatically in the US food supply in the past 60 years [23]. Adipose tissue concentrations of linoleic acid have increased dramatically as well [24].

Compared with ARA, DHA synthesis requires additional elongation and desaturation steps and involves an additional organelle, the peroxisome [6,25]. As a result, conversion is extremely inefficient and highly variable. Women of reproductive age can convert up to 9% of alpha-linolenic acid to DHA [26]; however, at a typical alpha-linolenic acid intake of 1 g/d, US women could synthesize no more than ~90 mg/d of DHA, although the DHA need during pregnancy approaches 300 mg/d. The usual DHA intake of US women and synthesis meet less than half of this need, thus compromising fetal DHA accumulation [20].

Fatty acid synthesis is also influenced by the fatty acid desaturase genes, FADS1/FADS2. These genes code for the delta-5 and delta-6 desaturase enzymes required to synthesize LCPUFA. Single-nucleotide polymorphisms in FADS1/FADS2 influence both LCPUFA status and response to LCPUFA intake [27–31].

Roles of docosahexaenoic acid and arachidonic acid in the brain

A detailed discussion of the role of DHA and ARA in the central nervous system is beyond the scope of this article; however, several functional roles are plausible based on what is currently known and their concentration in membranes in the central nervous system. Individual phosphoglyceride classes (phosphatidylethanolamine, phosphatidylserine, phosphatidylcholine, and phosphatidylinositol) in brain cerebral gray and white matter have unique LCPUFA profiles. ARA greatly exceeds DHA in inositol phosphoglycerides, whereas DHA exceeds ARA in serine phosphoglycerides [17]. Both of these phosphoglyceride classes are important in signal transduction; for example, inositol phosphoglycerides are key to the phosphatidyl inositol-3-kinase/Akt pathway [32] and phosphatidyl inositol 4,5-bisphosphate signaling [33], whereas serine phosphoglycerides are important for long-term potentiation [34]. It has been shown that animals with lower DHA status have less brain serine phosphoglyceride, and that DHA intake can increase brain serine phosphoglyceride concentration and long-term potentiation (a process critical to memory formation) [34].

In addition to their roles in brain phosphoglycerides, LCPUFAs are precursors for physiologically important metabolites, including prostaglandins, leukotrienes, and more recently discovered families of oxygenated metabolites including resolvins, which reduce inflammation through nuclear factor kappa B signaling [35–37]. DHA and ARA are also precursors of the endocannabinoids $\mathcal{N}$-docosahexaenoylethanolamide and anandamide, respectively, which are modulators of the central and enteric nervous systems [38–40]. For example, $\mathcal{N}$-docosahexaenoylethanolamide has been shown to promote hippocampal development [38] and anandamide to modulate spatial memory after stress [40]. In addition, DHA and AA and their metabolites are ligands for the nuclear receptor, peroxisome proliferator-actvated receptor gamma (PPARγ) [41,42]. All of these metabolites could influence physiologic functions of organs and tissues, and all have the potential for long-term effects on brain function and behavior (programming).

Given the clear role of LCPUFA in the brain, much interest has been generated about the effect of DHA and ARA on brain development and cognition in infancy and early childhood. We posit that these effects may be best assessed and understood from a perspective informed by the principles of early brain development and the nature of early assessment. These issues are addressed later in this article.

Brain development and assessment in infants and children

Brain development occurs in fairly specific stages during early life. By the end of the embryonic period (ie, the first 8 prenatal weeks), the fundamental structures of the brain and central nervous system are fairly well defined [43], and neurogenesis has begun [44]. As neurons are generated, they migrate to their final positions in the brain, guided along distinct pathways by specialized adhesion molecules on cell surfaces, or by crawling along radial glia [45]. Once neurons have finished migrating, 2 processes occur. First, dramatic neuronal growth forces brain surfaces to become contorted within the finite space of the skull; this results in the characteristic ridges (sulci) and folds (gyri) seen in the mature brain. Second, neurons engage in arborization, a process through which the dendrites of an estimated 100

billion neurons [46] form up to 1000 functional connections (synapses) with the axons or terminal branches of other neurons [43]; this rich and dense network of interconnections mediates all forms of behavior and cognition seen in the organism across the life span. This dendritic branching continues to occur postnatally [47]; so much so that neural connections that prove to be redundant or less used during the course of the organism's experience or behavior are "pruned" [48,49] and superfluous neurons die off and are resorbed. The final step in brain development is the emergence of myelin [50], a fatty substance that wraps axons and increases the efficiency of neural transmission. Bundles of myelinated axonal fibers appear as mature white matter tracts or pathways, as opposed to unmyelinated gray-matter fibers [43]; again, myelination occurs at different schedules in different parts of the brain.

Note that although genetic influences contribute in obvious ways to the initiation and organization of the program for brain development, exogenous forces strongly determine much of the ultimate structural and functional characteristics of the central nervous system. Maternal environment can meaningfully affect even the earliest processes of central nervous system development, including neurogenesis [51], neuronal migration [52], and synaptogenesis [53]. Depending on the timing and dose of experiences, the effects of these early maternal or environmental conditions can be powerful in their influence on the long-term developmental outcome of offspring. The disproportionate effects of such influences on early prenatal and postnatal life gave rise to the concept of prenatal and early postnatal life as critical periods [54] for determining later development. In the dietary or nutrition literature, the lasting nature of such effects is often considered to reflect early developmental programming of later cognitive or behavioral outcomes [55–57].

The cycle of neurogenesis, migration, synaptogenesis, and pruning characterizes brain development at the cellular level, but, for understanding behavioral and cognitive development, considerations from a more structural perspective are also critical. Between the third and fifth weeks of prenatal life, the neural tube differentiates structurally into distinct structural components that give rise to the brain stem, midbrain, and cerebral cortex. Most brain stem (eg, pons, medulla) functions are related to the maintenance of vital (respiratory, cardiovascular, sleep-wake, and other autonomic) characteristics. Midbrain (eg, thalamus, hypothalamus, amygdala) functions are related to processing sensory input and motivating behavioral responses related to basic survival and reproductive needs. More complex and flexible forms of behavior and cognition are mediated by integration of controlling cerebral structures with lower-order cognitive functions. However, behavior and cognition are rarely governed by the activity of a single area or structure; behavior and cognition may be best considered as derivatives of interactions among these 3 structural levels. However, because the 3 structural levels have distinct developmental courses, behavioral and cognitive development necessarily reflect the interaction of these systems at different stages of maturity [58]. Furthermore, maturation within structural levels (particularly within cerebral and cortical pathways) also follows distinct and dissociable developmental courses. For example, lower-order (and phylogenetically earlier) senses such as olfaction, taste, and touch emerge earlier than audition, and vision follows after that; vision has a protracted developmental course that extends into the third postnatal year [59]. Following on sensory development, cerebral structures generally mature in a posterior-to-

anterior direction with the frontal areas of the cerebrum maturing last [60]. Thus, simple forms of cognitive functions such as attention and memory emerge early but become increasingly interrelated and integrated as the frontal lobes mature, and this integration leads to the emergence of increasingly complex forms of cognition, such as goal-directed behavior, strategic planning, reasoning, and other executive functions [61]. Modern models of the emergence of specific cognitive abilities suggest that repeated use of particular neural circuits (ie, through practice or simple repetition) results in the parcellation of brain areas devoted to those abilities; in turn, this makes such abilities independent and dissociable, thus giving the appearance of cognitive modularity [62,63].

The conceptualization of behavioral development has important implications for how clinicians choose to measure early cognition. A common strategy in quantifying behavioral development in infancy and early childhood involves the assessment of whether the emergence of an individual child's common, global motoric responses (eg, sitting up, crawling, walking) matches with the normal or typical developmental course (as derived from a standardized sample). Slightly more sophisticated assessments may tap whether other, more complex behavioral responses (eg, imitation, word production, following instructions) are behind, at, or ahead of a similar normative schedule. However, given the conceptualization of behavioral and cognitive constructs from the principles of brain development described earlier, these global measures (particularly in infancy, when systems are immature) are unlikely to relate to or signify long-term outcomes, and the global nature of such measures may obscure deficiencies (or, for that matter, advantages) in the function of specific brain systems during development [64].

Over the last several decades [65] developmental scientists have generated strategies for tapping into more targeted and specific measures of cognitive abilities in infancy and early childhood. One of the advantages of this approach is that, if the effects of an environmental or organismic condition/status are more specific, measurement of that specific skill (eg, attention, memory, inhibition) is more likely to reveal an effect. Another important advantage is that measurement of specific cognitive constructs or systems may be more likely to be related to longer-term outcomes than a global measure that conflates the contribution of many systems or cognitive constructs, some of which may be irrelevant to longer-term outcomes. Recent empirical findings implicate specific and targeted cognitive measures taken during infancy in both direct [64,66] and indirect [67,68] prediction models of cognitive outcomes in childhood.

Cortical visual acuity

Cortical visual acuity was the first brain function studied in preterm infants to determine whether DHA would improve development. Both electrophysiologic [69] and behavioral outcomes [70] were measured. Subsequently, several masked clinical studies compared commercially available infant formulas without DHA and ARA with formulas with DHA and ARA and showed higher visual acuity in both term and preterm infants (see Ref. [71] for review). Most studies stopped assessing visual acuity at 12 months of age or earlier, but Birch and colleagues [72] studied 4-year-old children and found poorer visual acuity in the group that was not fed LCPUFA in infancy, but similar visual acuity in groups fed DHA or

DHA plus ARA, compared with the group that was breast-fed. Based on these studies, EFSA allowed the claim that DHA contributes to the visual development of infants from birth to 12 months so long as the formula contained at least 0.3% of total fatty acids as DHA [12]. The most recent study of visual acuity in supplemented infants was from a large dose-response study (0.32%, 0.64%, or 0.96% total fatty acids as DHA and 0.64% as ARA compared with a formula without DHA and ARA). The DIAMOND trial began in 2003 and was conducted at 2 sites in the United States (Dallas, TX, and Kansas City, MO). DHA and ARA supplementation significantly enhanced visual acuity at 12 months of age, confirming earlier studies. The study found similar benefit of LCPUFA-containing formula for visual acuity at 12 months of age compared with formula without LCPUFA regardless of DHA dose [73].

Cognition

In addition to visual acuity, the high accumulation of DHA and ARA in brain has prompted substantial interest in the effects of these LCPUFAs on cognition. The first evidence that DHA could improve cognitive function was reported in 1996 from 2 studies in very low birth weight preterm infants, 1 with DHA and EPA supplementation to 2 months corrected age (CA) and 1 with DHA and EPA supplementation to 9 months CA. In both studies infants had significantly shorter duration looks during a fixed time to test [74,75], which reflects more rapid visual information processing [76]. Shorter duration looks at 12 months CA in infants supplemented only to 2 months CA was also the first evidence that improving DHA status during early development could program higher cognitive function long after supplementation is discontinued [74]. Shorter duration looking was also later observed in monkeys fed a standard nursery diet with alpha-linolenic acid compared with a diet deficient in omega-3 fatty acids.

Children from the Kansas City cohort of the DIAMOND trial had lower heart rates when fed formula with DHA and ARA compared with formula without DHA and ARA, but no dose-response effect was observed [77]. The groups of infants fed 0.32% and 0.64% DHA showed higher quality attention, spending more time engaged in active stimulus processing (sustained attention) than the group fed the control formula. The group fed 0.96% DHA had a response that was intermediate between the control and 0.32%/0.64% groups and did not differ significantly from these groups [77]. The authors then conducted age-appropriate tests of development on the children in each group every 6 months from 18 months to 6 years of age [78]. Positive effects of DHA and ARA supplementation were observed on rule-learning and inhibition tasks when the children were between 3 and 5 years of age, and on standardized tests of vocabulary and verbal intelligence quotient (IQ) at 5 and 6 years of age (Peabody Picture Vocabulary Test and Weschler Primary Preschool Scale of Intelligence) [78]. With the exception of 1 task (requiring the child to inhibit a prepotent response to a stimulus), the group fed 0.96% DHA/0.64% ARA performed less well than the 0.32% and 0.64% DHA groups but better than the control group (although not significantly different from either). A 6-country study in Europe of formula-fed infants also found cognitive benefit (faster information processing) at 6 years of age in children who were fed formula with 0.2% DHA and 0.35% ARA for only 4 months in infancy compared with a control formula without LCPUFA [79]. These results in young children are consistent with several

earlier reports showing advantages of early developmental exposure to higher DHA intake during pregnancy and/or with human milk feeding that also provided ARA to the developing fetus/newborn [80,81].

In general, the results of studies show benefit or no effect on cognitive function at school age of early exposure to higher DHA or DHA plus ARA. However, a Danish study that supplemented lactating women who were low fish consumers with a high-dose fish oil compared with olive oil found poorer performance in the fish oil group at age 7 years: processing speed was slower overall and a measure of prosocial behavior was lower in boys [82]. However, the investigators did not publish the results of the human milk fatty acid composition; it would be interesting to know whether DHA was present in great excess relative to ARA.

Several studies of the effects of DHA or DHA plus ARA supplementation on cognition have been conducted in very low birth weight infants at school age. A study in Norway that provided DHA and ARA supplementation to human milk until discharge from the hospital found no effect of the randomization on several tests at 20 months [83] or on cognitive function or brain macrostructure on MRI at age 8 years [84]. A large cohort from the Australian DHA for the Improvement of Neurodevelopmental Outcome in Preterm Infants (DINO) trial compared neurodevelopment at 7 years of age in children who were fed ~0.35% DHA compared with 1% DHA until term CA and found no evidence of benefit; however, group mean scores on the Wechsler Abbreviated Scale of Intelligence were high, ranging from 98.0 to 98.8 for both the primary and secondary assessments of IQ [85]. A study from the United Kingdom found some positive results at 10 years of age for infants fed 0.5% DHA in formula from birth to 9 months of age for verbal IQ, full-scale IQ, and memory; and benefits for literacy in girls [86]. With the exception of Isaacs and colleagues [86], the studies were of short duration and the control groups were receiving the same LCPUFA as the intervention group, making it impossible to conclude that these infants did not benefit from DHA or DHA plus ARA. The control groups in 2 of these studies seem to have been provided adequate LCPUFA.

Not all cognitive domains tested in the Kansas City cohort of the DIAMOND trial showed behavioral effects of DHA and ARA. For example, spatial memory and advanced problem solving were not influenced by early DHA and ARA intake. Neither were early tests of global development such as the Bayley Scales of Infant Development (BSID) and the MacArthur-Bates Communicative Developmental Inventory [78], which were designed to determine whether infants and young children are meeting normal milestones of development. In contrast, DHA-supplemented and ARA-supplemented children from the Dallas cohort of the DIAMOND trial, with different demographics, scored 5.7 points higher on the BSID Mental Developmental Index at 18 months [87], but had poorer receptive vocabulary at 2 years (although not at 3.5 years) [88]. Global tests of development generally have similar null findings to ours and serve as the main basis for 4 systematic reviews that conclude either (1) that there is no benefit of LCPUFA supplementation in infancy to cognitive development, or (2) that there is insufficient evidence to conclude that an effect exists (see Ref. [89] for commentary). However, there are fewer studies that have assessed targeted tasks so these do not lend themselves to systematic reviews.

Brain electrophysiology and studies in childhood

In addition to measuring behavior, this article has discussed brain electrophysiology in the DIAMOND cohort, measuring evoked response potentials (ERPs) during a Go–No-go task at 5.5 years in which children were asked to press a button only if a fish appeared but to inhibit button press if a shark appeared. Children fed DHA and ARA during infancy compared with the control group showed a distinct N2 amplitude response to No-go versus Go trials before the button press that the authors interpret as engagement of more mature inhibitory control [90]. Children fed DHA and ARA also showed a unique microstate during No-go trials that was consistent with involvement of frontal structures on the inhibition of a response. More recently, the authors have studied about half of the cohort at 9 years of age using structural, functional, and metabolic studies of brain: MRI, magnetic resonance spectroscopy, and magnetoencephalography (manuscript in preparation). In both ERP and subsequent brain imaging studies at 9 years, the 0.64% DHA/0.64% ARA group consistently has the most mature brain performance and differs most from the control group.

Grayson and colleagues [91] recently reported that cortical interconnectivity in the brain of adult rhesus macaques exposed to a lifetime of omega-3 fatty acids intake was similar to organization in healthy human brain but different from that of macaques exposed to a lifetime of an omega-3–deficient diet.

Single-nucleotide polymorphisms and cognition

As mentioned earlier, there are genetic differences in ability to synthesize ARA and DHA from the 18-carbon essential fatty acid precursors. An intriguing possibility suggested by the recent work of Peters and colleagues [92] is that individuals with fatty acid desaturases (FADS) minor alleles have poorer quality brain white matter development, which affects brain function. Martinez and Vazquez [93] first showed a link between brain DHA accumulation and myelination in children with peroxisomal disorders who are unable to synthesize DHA, so differences in LCPUFA synthesis could theoretically decrease brain myelination. Limitations in LCPUFA synthesis could thus indirectly affect brain myelination.

Three studies have investigated the relationship between 1 FADS2 polymorphism (rs174575) and IQ in cohorts of children or adults who were fed either human milk (which contains cholesterol as well as omega-3 and omega-6 LCPUFAs) or formula in infancy (before the addition of DHA and ARA to infant formula) [94–96]. In all 3 studies the groups that carried 1 or both major alleles had higher IQs if they were fed human milk compared with infant formula. Rizzi and colleagues [96] were the only group of investigators to control for parental education, which attenuated the effect of human milk on IQ. If there is an advantage of human milk feeding for major allele carriers, both dietary LCPUFA and cholesterol could be invoked and neither can be ruled out. In contrast, none of these studies showed enough difference among the FADS allele groups fed formula to suggest an effect of FADS allele on IQ. What is intriguing is that in 2 of these studies there is no obvious increase in IQ with human milk feeding in individuals homozygous for the minor allele [94,96], whereas Steer and colleagues [95] found that minor allele homozygotes had the lowest IQ with formula feeding and the highest IQ when fed human milk. The data available

at this time are difficult to interpret and may depend on a better understanding of how LCPUFA synthesis is controlled; for example, it has been reported recently that FADS2 contains a sterol regulatory element [97]. There may be undiscovered links between LCPUFA and cholesterol that influence the response of the developing brain to variations in LCPUFA and cholesterol intake.

Allergy and immunity

Higher omega-3 LCPUFA intake is associated with lower allergy incidence in several studies, including those of Duchen and colleagues [98,99]. A recent Scandinavian study linked minor allele carriers of several FADS alleles associated with lower blood ARA with reduced risk of atopic eczema but not respiratory allergy at age 13 years [100]. Several studies have looked at immune function or allergy in groups of infants randomly assigned to different LCPUFA intakes. Field and colleagues [101] found that infants fed formula with DHA and ARA had immune cells and cytokine profiles more similar to infants fed human milk and different from infants fed formula without LCPUFA. Two US studies show lower allergy incidence in young children randomly assigned to formula with DHA and ARA compared with formula without LCPUFA during infancy [102,103]. Birch and colleagues [102] analyzed combined studies of formulas containing ~0.3% DHA and 0.6% ARA that were fed for varying periods of time during infancy. They found fewer medically documented allergic illnesses in the first 3 years of life in children receiving formula with compared with without LCPUFA. Similarly, the authors recently reported fewer medically documented allergies in the first 4 years of life with formulas containing DHA (0.32%–0.96%) and ARA (0.64%) compared with formula without LCPUFA [103]. When the authors assessed predictors of skin allergy and wheeze/asthma, we found an interaction with maternal allergy: LCPUFA protected against skin allergy in children of women who did not report allergy and against wheezing/asthma in children of women who reported allergy [103]. There is a need to determine when in development LCPUFA is important for reducing allergy [104–106].

Body composition

It is well known from animal and cell models that the omega-6 fatty acids, linoleic acid, and ARA are adipogenic [107,108]. Casado-Diaz and colleagues [41] reported that ARA, but not omega-3 LCPUFA (DHA and eicosapentaenoic acid [EPA; 20:5–3]) induce adipogenesis of human mesenchymal stem cells. In addition to serving as a reservoir for DHA, adipose tissue DHA accumulation in the fetus may play a role in programming body composition in childhood by counteracting the effects of omega-6 fatty acids. Moon and colleagues [109] reported an association between pregnancy DHA status and higher lean mass in childhood; and higher ARA status and higher fat mass in childhood using DXA. Using Bod Pod assessments, the authors found significantly higher fat-free mass in 5-year-old children (n = 78) whose mothers were randomly assigned to a DHA supplement of 600 mg/d during pregnancy compared with children of women assigned to a placebo of soybean and corn oils (n = 75) (presented at the ninth World Congress of the Developmental Origins of Health and Disease, Cape Town, South Africa, 2015).

The Imact of Nutritional Fatty Acids During Pregnancy and Lactation for Early Human Adipose tissue Development (INFAT) study conducted in Germany provided 1200 mg of omega-3 LCPUFA to pregnant women during the last 2 trimesters of pregnancy and the first 4 months of lactation. The supplement dramatically increased omega-3 LCPUFA exposure of the fetuses/infants [110]. Much and colleagues [110] found a significant positive relationship between the sum of 4 skinfold measurements at 1 year and maternal milk omega-3 LCPUFA at 6 weeks postpartum, in apparent contrast with the reports discussed earlier. The authors recently reported that children fed formula with DHA and ARA compared with no LCPUFA had higher length/stature and weight-for-age percentiles from birth to 6 years of age, but no increase in body mass index [111]. We speculate that increased DHA intake during pregnancy and infancy in populations with low DHA intake, such as the US population, may program early lineage of fetal mesenchymal stem cells resulting in higher fat-free mass relative to fat mass in the offspring. More work in this area is needed, including research using validated measures of body composition to understand how body composition in infancy influences body composition in childhood.

Assessment of the literature on docosahexaenoic acid and arachidonic acid and infant development

This assessment of the importance of DHA and ARA in infancy is biased toward US studies of infants randomly assigned to formula with DHA plus ARA compared with formula without LCPUFA. There are few such studies and US studies are overrepresented. As noted earlier, meta-analyses do not support benefits of DHA and ARA addition to infant formula, consequently it is not universally accepted that infants benefit from the addition of DHA and ARA to infant formula. The focus is on US studies in this article because (1) systematic reviews of published results rely heavily on a single test of global neurodevelopment designed to determine whether infants are meeting normal milestones of development, rather than on specific and more granular measures of cognitive constructs in infancy and early childhood [89]; (2) most studies of DHA and ARA supplementation have been conducted in countries where adults, including presumably women in their reproductive years, consume significantly more DHA than do women in the United States; and (3) few trials have followed children to ages at which the results of sophisticated tests of cognition or brain structure/function tests can be and are obtained.

DHA and ARA are nutrients, and a strong case can be made that DHA intake is inadequate in the US adult population [112]. As well, the positive effects of DHA and ARA supplementation on cognition, allergy incidence, growth, and body composition noted here for US children exposed to higher DHA or DHA plus ARA during development could not be found in an LCPUFA-sufficient population. There is no reason to suspect that studies that find no effect of LCPUFA supplementation are wrong; however, the authors do not regard meta-analyses as an ideal way to determine whether a nutrient deficiency needs correcting in a given group for DHA any more than, for example, for iron. The case for studying the effects of DHA in populations that are deficient in DHA has already been made [113].

In the past 10 years, there have been numerous articles published on the FADS alleles. It is now understood that among individuals there is a range in ability to synthesize LCPUFA,

and this is an important advance. However, this article does not focus much on FADS alleles even though they probably play a role in some of the inconsistencies in individual and group responses to LCPUFA supplementation found in the studies discussed here.

Researchers now have access to techniques to measure brain electrical interconnectivity and brain structure and function; these techniques were not used in the early studies of DHA and ARA supplementation. Positive effects of perinatal DHA and ARA exposure were observed in the DIAMOND study cohort that suggest that early DHA and ARA exposure in infancy resulted in more coherent and engaged brain function long after children were weaned to a standard US diet that was, incidentally, low in DHA [90]. More recent results from a subset of this cohort who underwent studies of brain structure, function, and metabolism show persistent positive effects of supplementation at 9 years of age (manuscript in preparation). The authors think that there is great potential for more direct studies of the brain because even the most targeted behavioral tests of cognition may underestimate the true effects of proper LCPUFA balance on brain functioning. We hope others will study older children and young adults from cohorts exposed to DHA and ARA early in development. Such studies should involve interdisciplinary teams of investigators, including investigators with expertise in brain structure, function, electrophysiology, and metabolism.

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Key points

- Docosahexaenoic acid (DHA), an omega-3 polyunsaturated fatty acid, and arachidonic acid (ARA), an omega-6 polyunsaturated fatty acid, are nutrients that were first added to formulas in the United States in 2002.
- DHA intake is low in the US population and this has implications for development.
- Early studies found more mature cortical visual function in infants fed formulas containing DHA and ARA and this led to a claim for improved visual acuity after these fatty acids were added to infant formula.
- Recent studies found positive effects of feeding DHA and ARA in infancy on cognition, brain connectivity, and allergy in early childhood, which provides evidence that these fatty acids program cognitive and immune development.
- The optimal balance of DHA and ARA intake during infancy is still not known, but current best practice suggests that the amount of DHA in infant formula should not exceed the amount of ARA.
- The effect of DHA and ARA status and supplementation in infancy has been largely evaluated through global developmental assessments focused on attainment of normative milestones, although more granular measures of specific cognitive function may be more sensitive markers of these effects.