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Commentary

Dietary arachidonic acid in perinatal nutrition: a commentary

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Arachidonic acid (AA) is supplied together with docosahexaenoic acid (DHA) in infant formulas, but we have limited knowledge about the effects of supplementation with either of these long-chain polyunsaturated fatty acids (LCPUFA) on growth and developmental outcomes. AA is present in similar levels in breast milk throughout the world, whereas the level of DHA is highly diet dependent. Autopsy studies show similar diet-dependent variation in brain DHA, whereas AA is little affected by intake. Early intake of DHA has been shown to affect visual development, but the effect of LCPUFA on neurodevelopment remains to be established. Few studies have found any functional difference between infants supplemented with DHA alone compared to DHA+AA, but some studies show neurodevelopmental advantages in breast-fed infants of mothers supplemented with n-3 LCPUFA alone. It also remains to be established whether the AA/DHA balance could affect allergic and inflammatory outcomes later in life. Disentangling effects of genetic variability and dietary intake on AA and DHA-status and on functional outcomes may be an important step in the process of determining whether AA-intake is of any physiological or clinical importance. However, based on the current evidence we hypothesize that dietary AA plays a minor role on growth and development relative to the impact of dietary DHA.

Lipids play varied and critical roles in metabolism, and their function is modulated by the individual fatty acid moieties. Membrane function has been shown to be modulated by the fatty acid composition of the phospholipids. Saturated and monounsaturated fatty acids represent the richest energy sources, whereas the essential n-6 and n-3 polyunsaturated fatty acids (PUFA) are the most biologically active fatty acids. The long-chain PUFAs (LCPUFA), arachidonic (AA), eicosapentaenoic (EPA), and docosahexaenoic acid (DHA), are incorporated into membrane phospholipids, precursors of signaling molecules (e.g., eicosanoids and docosanoids), and potent activators of a number of gene transcription factors (e.g., peroxisome proliferator activated receptors). Perinatal intake and maternal transfer of LCPUFA may therefore have an impact on growth, development, and susceptibility to diseases.

A distinctive feature of the intrauterine and neonatal period is that DHA is incorporated in high levels in the membranes of the central nervous system and this is in part dependent on maternal and infant diet. AA is incorporated into the membranes of all tissues in almost equal amounts and is less dependent on diet. AA has been shown to be readily taken up and incorporated into brain phospholipids and subsequently released upon activation of phospholipase A_2 with a possible role in brain signaling (1). However, the role of dietary AA-intake relative to infant development is still not well defined. In this commentary, we will discuss indirect as well as direct evidence of the role of AA in growth and development. As AA is often supplied together with DHA, we also discuss the effect of DHA in order to try to disentangle the effect of these LCPUFAs.

MATERNAL–FETAL TRANSFER OF ARACHIDONIC ACID

In the last weeks of pregnancy, LCPUFAs accumulate in the fetus and tend to reach higher concentrations in fetal/neonatal plasma than in the mother (2). So far, synthesis of LCPUFA has not been shown to occur in the placenta and most of the n-3 and n-6 LCPUFA acquired by the fetus is thought to come from the maternal circulation across the placenta through a facilitated diffusion process (3). Transfer of DHA across the placenta involves specific binding and transfer proteins facilitating the higher concentration of DHA in fetal compared with maternal plasma (4). AA-concentrations are also higher in the fetus, whereas concentrations of linoleic acid (LA) and α-linolenic acid (ALA) in maternal and infant blood differ much less (5,6). The phenomenon of increasing LCPUFA in the fetal department has been described as "biomagnification" (7), but could also be interpreted as a natural consequence of a dual liver system (i.e., the combined PUFA-metabolism of the mother and the fetus/infant).

In the third trimester, fetal growth is accompanied by deposition of fat tissue, which contains AA and DHA, although in more limited amounts than previously believed (8,9). On the other hand, LCPUFAs are also deposited in large amounts relative to the accretion rates of other fatty acids in the fetal brain during the period of maximum brain growth, which lasts through the first years of postnatal life (8,10). It has been estimated that fetal PUFA-accumulation is supported by a supply of ~50 mg/(kg × day) of n-3 PUFA and 400 mg/(kg × day) of n-6 PUFA (11). In both growth-retarded fetuses (IUGR) and

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infants born preterm, the progressive accumulation of n-6 and n-3 PUFA in fetal tissues is truncated at the end of pregnancy. The differences observed in the relative fetal–maternal relationships for AA and DHA associated with IUGR-pregnancies could also be related to a lack of LCPUFA-generating enzyme systems in the fetus, or impairments in the placental transfer of LCPUFA, and could potentially contribute to the neural and vascular complications that are associated with IUGR (12).

A few case–control studies have been conducted to evaluate whether maternal and fetal n-3 and n-6 PUFA-status might play a role in the pathogenesis of preterm birth. Women who deliver preterm have been demonstrated to have higher levels of AA and other n-6 LCPUFA in their blood and trophoblast tissue compared to women who deliver at term (13). Furthermore, maternal dietary supplementation with marine n-3 LCPUFA has been shown in randomized controlled trials (RCT) to reduce the risk of early preterm delivery (<34 wk) (relative risk = 0.74; (95% confidence interval = 0.58, 0.94)) and result in a modest increase in birth weight (14). Due to the role of AA-derived eicosanoids in the initiation of delivery it is biologically plausible that a slight dampening of this effect by competition with n-3 LCPUFA could explain a protective effect of n-3 LCPUFA against the risk of early labor (15). It could even be speculated that the relatively lower fetal accumulation of AA relative to DHA is due to the need for the placenta to retain AA to initiate prostaglandin production and delivery. However, overall the mechanisms involved in placental transfer of LCPUFA remain unclear, and the extent to which the liver in the developing fetus contributes to the overall accumulation of LCPUFA in fetal membranes through endogenous synthesis from the precursors also requires clarification.

BREAST MILK ARACHIDONIC ACID CONTENT

Infant blood PUFA-levels remain higher than maternal levels for some time postnatally especially in the breast-fed infant (16,17). Whereas the erythrocyte (RBC) DHA-status of breast-fed infants has been found to be associated with maternal RBC DHA-status during lactation, no such association was observed for AA (18). Breast milk LCPUFA-levels, i.e., the absolute quantities of DHA and AA, seem to be quite stable throughout 12 mo of lactation (19). Considering DHA and AA-concentrations in breast milk worldwide, Brenna *et al.* (20) showed that the mean concentration of DHA was 0.3 ± 0.2% and that of AA was 0.5 ± 0.1%. The correlation between breast milk content of DHA and AA was surprisingly low with a high degree of variability in the ratio of DHA to AA in individual breast milk samples. It is noteworthy that the SD of breast milk DHA is >50% of the mean value, whereas that for AA is around 30%. The higher variability of DHA is consistent with the conclusions of another review (21), which reported that although mean breast milk levels of AA were very similar in all countries, ranging from 0.36% to 0.49%, mean DHA-levels ranged from 0.17 to 0.99%, with the highest levels in Japan and the lowest in samples from Canada and the USA. Typically, breast milk has 1.5- to 2-fold more AA than DHA, but in countries with a high fish consumption the DHA-content may be higher than that of AA. The AA/DHA-ratio in breast milk is therefore high in mothers who consume little fish and low in mothers with high n-3 LCPUFA-consumption. It has been shown that the DHA-level in breast milk is directly related to the DHA-content of the maternal diet (22), but it is not known if the lower variability in breast milk AA is explained by metabolic or dietary mechanisms. Breast milk AA was not affected in lactating mothers who were allocated to consume increasing doses of DHA (22) or 3 g/d DHA-rich tuna oil (23) to achieve a breast milk DHA-concentration of around 1% of the fatty acids. Two recent studies confirm the different regulation of AA and DHA in breast milk, indicating that AA is affected by the genetic pattern in the *FADS*-gene cluster (24) and less sensitive than DHA to dietary supplementation (25).

BRAIN COMPOSITION IN INFANCY—INFLUENCE OF DIET

On the whole, membrane PUFA-composition (the principal components of which are LA, AA and DHA) seem to be more responsive to LA and DHA in the diet than to intake of AA. Animal studies have demonstrated that an increase in dietary n-3 PUFA as ALA is almost completely reflected in the membrane n-3/n-6 PUFA-ratio in tissues at LA/ALA intakes of <10, whereas the dietary balance between ALA and LA has little influence at higher ALA intakes and a similar biphasic response is also seen in diets that contain LCPUFA (26). These results show a high sensitivity of brain membranes to dietary variations in the PUFA-supply within the normal range, strongly favoring incorporation of n-3 LCPUFA over LA and AA. In neonate baboons, dietary DHA consistently supported greater brain DHA-incorporation and maintenance of cortex DHA-concentration with feeding duration, while brain AA was not related to the dietary supply and decreased with age in all tissues (27). In the case of a dietary deficiency of n-3 PUFA, there is a trend for DHA to be replaced with the nearest n-6 PUFA equivalents, whereas few changes are seen for the reciprocal lack of dietary of n-6 PUFA (28,29). Thus, n-3 PUFA seems to be the main determinant of the membrane PUFA-composition and the data are consistent with the hypothesis that brain membranes are regulated towards a high level of unsaturation.

Cerebral structures accumulate n-6 and n-3 PUFA during the perinatal period and early infancy. Although the brain, in common with most tissues, accumulates considerable amounts of AA, DHA appears to accumulate preferentially in neural structures. High deposition rates of DHA in the third trimester have been calculated and derived from postmortem studies and the average whole-body DHA-accretion during this period amounts to around 50 mg/d. The accretion of AA is approximately double (100 mg/d), but the relative measure (i.e., % of fatty acids) indicates a preferential accumulation of DHA in brain compared to AA (8). In the mid-1990's, two research groups investigated PUFA-accumulation in brain autopsies from human infants who had died of Sudden Infant Death Syndrome in the first months of life. The UK group (30) found that the mean cortical phospholipid weight % of DHA was around 25% greater in five breast-fed infants (9.7%) compared to five age-comparable formula-fed infants (7.6%).

However, the overall percentage of LCPUFA was maintained in term formula-fed infants and the reduction in DHA was compensated for by a significantly increased incorporation of all the dominant n-6 PUFA. However, in formula-fed preterm infants with the lowest concentration of cortical DHA, this compensatory effect in n-6 PUFA was only partial and an increase in the n-9 series PUFA was also detected. The second autopsy study of brain tissue from Australia (31) found a greater proportion of DHA in both RBC and brain cortex in term breast-fed infants relative to those who were formula-fed. Furthermore, cortex DHA increased with age in breast-fed but not in formula-fed infants. In contrast to DHA, the percentage of AA in the brain increased with age to a similar extent in all infants, irrespective of diet. Observations in human infants are thus consistent with experimental data in infant baboons, showing that brain DHA-levels are responsive to diet, while AA-levels are not. The question therefore arises whether lack of preformed dietary AA would result in lower brain AA or if it might be obtained from body stores or by synthesis from LA as suggested by the autopsy data (32).

DIETARY ARACHIDONIC ACID, POSTNATAL GROWTH AND DEVELOPMENT

Support for the concept of the essentiality of AA in infant nutrition came from the observation of potentially adverse effects in preterm infants of a marine-oil containing formula (0.5% n-3 LCPUFA of which 0.3% was EPA, which thus dominated over DHA) (33). In this study, plasma phosphatidylcholine AA-concentration was found to correlate with measures of normalized growth, which led the authors to hypothesize that AA deficiency may contribute to decreased growth in preterm infants over the first year of life (33). Earlier observational data had also shown a positive correlation between body weight and postnatal plasma triglyceride AA (and total n-6 PUFA) and an inverse correlation with ALA (34). These data do not, however, prove an essential role of dietary AA and furthermore have not been replicated in subsequent larger RCTs in preterm or term infants. In fact, formula LCPUFA-supplementation of preterm infants (who are potentially more sensitive to dietary changes, particularly in LCPUFA, than term infants) have not shown significant effects of supplementation on weight, length or head circumference ≥12 mo, as reported in a meta-analysis (35). The largest preterm DHA-supplementation RCT to date, which included both formula-fed and breast-fed infants and kept infant AA-intake constant, suggests that infants in the high-DHA group were slightly longer than infants in the standard-DHA group at 18 mo corrected age (23).

Overall, data from RCTs indicate no benefit on growth of maintaining a higher intake of AA relative to DHA as currently recommended for infant formulae (36). For term infants, few of the RCTs on formula LCPUFA-enrichment have investigated the effects of addition of DHA alone and, although this has been shown to decrease RBC-AA-status (37–40), the functional consequences of the decrease are not clear. The majority of the RCTs investigating the effect of dietary LCPUFA-supplementation in term infants have added both AA and DHA, although some have varied DHA-intake at a constant intake of AA. Overall, meta-analyses of these trials have shown no effect of LCPUFA-supplementation on physical growth throughout the first 3 y of life irrespective of the type of LCPUFA-supplementation, duration of supplementation and method of outcome assessment (41,42). However, the heterogeneous study designs with respect to doses, supplementation strategies, group size and methodologies for primary outcome assessment complicate attempts to combine data in meta-analyses to achieve conclusions with respect to the functional consequences of the addition of LCPUFA, or the specific effects of AA addition. A meta-analysis of RCTs that supplemented lactating mothers with n-3 LCPUFA showed that infants of supplemented mothers were around 1 cm shorter at 2 y, but had larger heads at 1–2 y of age (43). Thus, although these studies do not allow for definitive conclusions about potential effects of dietary AA (44), they do not indicate that dietary AA is important for growth.

With respect to neural function, the most accepted developmental effect of LCPUFA-supplementation in infants is an increased rate of visual acuity development (45), which seems to be explained solely by DHA. Some of the RCTs in this field compared formulae with DHA and DHA+AA with a control formula without LCPUFA and found that the visual acuity of all supplemented infants was similar to that of human milk–fed infants, whereas that of the unsupplemented infants was significantly lower (37,46). A metaregression analysis also found that variability in the effects on visual acuity between studies was explained by the dose of DHA (47).

One RCT found that addition of AA to formula in a highly bioavailable form (egg phospholipids) resulted in RBC AA-concentrations that exceeded that in breast-fed infants (48) and observed a positive association between the AA/LA-ratio in RBC phosphatidylcholine and developmental test scores (Brunet-Lezine) at 24 mo. The effect was, however, independent of group allocation and could therefore be confounded (49). Another RCT in term infants that also varied formula DHA-concentrations (from 0.32 to 0.96%) at constant AA (0.6%) found that cognitive outcomes differed between all LCPUFA-groups and the control group, but not between groups given formula with different levels of DHA relative to AA (50,51). This might be interpreted as an effect of AA, but this conclusion is limited by the fact that no group received a formula with only AA. The largest available RCT in preterm infants, which as previously mentioned included both breast-fed and formula-fed infants that differed only in DHA-intake (0.35 vs. 1.0% at a constant intake of 0.6% AA), found a higher Bayley scale mental development index (MDI) and fewer girls with delayed mental development at 18 mo of age in the high-DHA group (23).

Since there are insufficient data to consider the effects of individual LCPUFAs, meta-analyses have considered the effects of AA and DHA together. Meta-analyses of all RCTs with neurodevelopmental outcomes at different ages throughout the first 2 y of life have not shown any statistically significant benefit of LCPUFA-supplementation of infant formula on the Bayley

scales of development in term or preterm infants (41,44,52). However, a trend for an effect on Bayley MDI at around 12 mo of age ($p = 0.06$) was shown in a meta-analysis that combined all LCPUFA formula supplementation trials in both term and preterm infants (52). This meta-analysis did not find any effect of prematurity on the efficacy of LCPUFA-supplementation nor did it find an effect of LCPUFA dose, although there was a trend towards an effect of DHA dose ($\beta = 9(-6; 23)$), without any such trend for AA ($\beta = -0.3(-7.9;7.3)$) (52). Meta-analyses looking at the developmental effects of maternal n-3 LCPUFA-supplementation in pregnancy and lactation have suggested some effects on neurodevelopment, but this was based on very few studies (43,53). It should be noted that the age at which the effects were examined in the different RCTs, both those with direct addition of LCPUFA to formula and maternal n-3 LCPUFA trials varied a lot, and that the effects in the first few years of life may not be representative of effects in the long term. These and other methodological aspects (e.g., the questionable use of the Bayley scales to detect differences within normally developing children) should be considered. It is at present not possible to draw any firm conclusions regarding the effects of either DHA or AA on mental performance.

A few RCTs have investigated the effect of LCPUFA-supplemented formulas on the development of allergy, with positive effects in some, but not all studies (54). It is, however, unlikely that these effects are explained by the addition of AA as other studies seem to indicate such effects in RCTs with maternal n-3 LCPUFA-supplementation, in agreement with the previously mentioned meta-analysis of all RCT of n-3 LCPUFA-supplemented lactating mothers (43) and other systematic reviews of the effect of perinatal n-3 LCPUFA-supplementation of mothers (45,46). Long-term follow-up studies of RCTs have found a possible role of maternal fish oil or fish intake on the offspring's risk of allergy, but the role of early dietary AA-supply in this context is not known (47,48).

ROLE OF GENETIC VARIABILITY IN LCPUFA LEVELS AND FUNCTIONAL RESPONSES

Applying current knowledge about the genetic control of LCPUFA-synthesis is a further way to derive indications for the dietary requirement for preformed LCPUFA in the perinatal period. Single nucleotide polymorphisms (SNPs) in the fatty acid desaturase (*FADS*) gene cluster have been shown to explain as much as 29% of the variation in serum AA-contents in adults, while serum DHA-concentrations were found to be primarily determined by the dietary supply of preformed DHA. Minor allele homozygotes of various *FADS* SNPs have also been found to have lower blood (RBC and plasma) levels of AA during pregnancy and consistently higher levels of LA and ALA (55,56). This is in line with findings in plasma from both mothers and neonates showing strong inverse associations between the minor allele for two *FADS* SNPs and concentrations of AA, EPA and DHA and furthermore suggesting that new-born infants had a greater capacity to synthesize AA than n-3 LCPUFA, although some synthesis of DHA was occurring as well (57). Curiously, a study of 2,000 cord blood samples found that minor allele *FADS* SNPs in the mother gave rise to increased levels of n-6 PUFA before the delta-5 desaturation step (LA and di-homo γ-linolenic acid), whereas minor allele SNPs in the child resulted in decreased levels of AA and other n-6 LCPUFA beyond this point in the metabolic pathway (58). Colostrum AA (and DHA)-levels have also been found to be decreased in minor allele carriers of a number of *FADS* SNPs (59), but studies in mature breast milk have shown that the concentration of AA is influenced to a larger extent by *FADS* polymorphism than that of DHA (20,50,57).

Overall, the data suggest that the n-6 PUFAs in breast milk, plasma and blood cell membranes across all ages are more affected by *FADS* polymorphisms than n-3 PUFAs, typically with an increase in LA and a decrease in AA-levels in minor allele carriers (55,56,60–63). However, we have recently found that *FADS* polymorphisms contributed substantially to DHA-status in late infancy, and some SNP minor alleles were even found to up-regulate DHA-status (60), whereas minor alleles of all the investigated SNPs lowered AA in a consistent way (64). Furthermore, a longitudinal study of serum phospholipid fatty acid composition at 2 and 6 y in 331 children found lower tracking of n-6 LCPUFA in children who were homozygous for the major allele of various *FADS* SNPs compared to the tracking that was seen in carriers of at least one minor allele, whereas the tracking in n-3 LCPUFA-levels was highest in major allele carriers (65).

Several studies have found associations between *FADS* haplotype patterns and neurodevelopmental outcomes in breast-fed vs. formula-fed infants although the observed effects currently appear to be somewhat inconsistent (59,65–67). The differences in the observations may be explained by the observed variable associations between different *FADS* SNPs and blood levels, especially for DHA (60) as indicated by the most recent studies (64,68). The importance of *FADS* genotypes has also been investigated in relation to plasma lipid profile in childhood (69,70) and atopic development, specifically of asthma (71–73). Furthermore, daily margarine intake (amongst the major sources of n-6 PUFA) has been found to be associated with increased asthma in children who were major allele homozygotes, indicating that *FADS* gene variants may modulate risk of allergic diseases possibly via a reduction in AA (72). Current knowledge about the functional effects of *FADS* polymorphism is still limited (74) and although most clearly associated with AA-status, functional associations with *FADS* genotype cannot be taken as proof of the role of AA. The influence of *FADS* polymorphisms on status—and specifically the observed variations between specific fatty acids and SNPs over time—introduces a new variable to be considered in the evaluation of the effects of LCPUFA-supplementations on the growth, development and health of young children.

CONCLUSION

The role of dietary AA in the perinatal period needs to be clarified and disentangled from the effects of DHA. To date, few studies have examined and/or found any difference between

the effects of DHA-supplementation alone to mothers or infants and the more customary DHA+AA-supplementation. AA in breast milk is less associated with maternal dietary habits and very stable throughout the world. Autopsy studies show a similar low variability in brain AA in breast-fed infants and dependence of DHA-levels on dietary intakes. It has been hypothesized that there may be synergistic as well as antagonistic effects between n-6 and n-3 LCPUFA and that it is important to aim at a balance to maintain tissue level homeostasis. While synergism might be a feature at low n-3 PUFA-status, AA becomes suppressed by antagonism at high levels of EPA+DHA (≥8% in RBC) (75). This level matches exactly the limit suggested as optimal in relation to prevention of cardiovascular diseases (76). However, it remains to be established if this is indicative of optimal function and health in infants. It also remains to be established if the potential effects of DHA are antagonized by n-6 PUFA and whether single addition of n-3 LCPUFA can positively affect neurodevelopment or decrease allergic and pro-inflammatory reactions later in life. Thus, the question about whether intake of preformed AA is of any importance (good or bad) is still unanswered and we hypothesize that it will have a minor role relative to the impact of dietary DHA on growth and development.

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REFERENCES

1. Duncan RE, Bazinet RP. Brain arachidonic acid uptake and turnover: implications for signaling and bipolar disorder. Curr Opin Clin Nutr Metab Care 2010;13:130–8.
2. Montes R, Chisaguano AM, Castellote AI, Morales E, Sunyer J, López-Sabater MC. Fatty-acid composition of maternal and umbilical cord plasma and early childhood atopic eczema in a Spanish cohort. Eur J Clin Nutr 2013;67:658–63.
3. Herrera E. Implications of dietary fatty acids during pregnancy on placental, fetal and postnatal development–a review. Placenta 2002;23:Suppl A:S9–19.
4. Gil-Sánchez A, Larqué E, Demmelmair H, et al. Maternal-fetal *in vivo* transfer of [13C]docosahexaenoic and other fatty acids across the human placenta 12 h after maternal oral intake. Am J Clin Nutr 2010;92:115–22.
5. Agostoni C, Galli C, Riva E, et al. Whole blood fatty acid composition at birth: from the maternal compartment to the infant. Clin Nutr 2011;30:503–5.
6. Oliveira OR, Santana MG, Santos FS, et al. Composition of fatty acids in the maternal and umbilical cord plasma of adolescent and adult mothers: relationship with anthropometric parameters of newborn. Lipids Health Dis 2012;11:157.
7. Crawford MA, Hassam AG, Williams G. Essential fatty acids and fetal brain growth. Lancet 1976;1:452–3.
8. Kuipers RS, Luxwolda MF, Offringa PJ, Boersma ER, Dijck-Brouwer DA, Muskiet FA. Fetal intrauterine whole body linoleic, arachidonic and docosahexaenoic acid contents and accretion rates. Prostaglandins Leukot Essent Fatty Acids 2012;86:13–20.
9. Kuipers RS, Luxwolda MF, Offringa PJ, et al. Gestational age dependent content, composition and intrauterine accretion rates of fatty acids in fetal white adipose tissue. Prostaglandins Leukot Essent Fatty Acids 2012;86:39–49.
10. Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Intrauterine fatty acid accretion rates in human brain: implications for fatty acid requirements. Early Hum Dev 1980;4:121–9.
11. Cetin I, Alvino G, Cardellicchio M. Long chain fatty acids and dietary fats in fetal nutrition. J Physiol (Lond) 2009;587(Pt 14):3441–51.
12. Cetin I, Giovannini N, Alvino G, et al. Intrauterine growth restriction is associated with changes in polyunsaturated fatty acid fetal-maternal relationships. Pediatr Res 2002;52:750–5.
13. Reece MS, McGregor JA, Allen KG, Harris MA. Maternal and perinatal long-chain fatty acids: possible roles in preterm birth. Am J Obstet Gynecol 1997;176:907–14.
14. Imhoff-Kunsch B, Briggs V, Goldenberg T, Ramakrishnan U. Effect of n-3 long-chain polyunsaturated fatty acid intake during pregnancy on maternal, infant, and child health outcomes: a systematic review. Paediatr Perinat Epidemiol 2012;26:Suppl 1:91–107.
15. Allen KG, Harris MA. The role of n-3 fatty acids in gestation and parturition. Exp Biol Med (Maywood) 2001;226:498–506.
16. Jørgensen MH, Nielsen PK, Michaelsen KF, Lund P, Lauritzen L. The composition of polyunsaturated fatty acids in erythrocytes of lactating mothers and their infants. Matern Child Nutr 2006;2:29–39.
17. Koletzko B, Schmidt E, Bremer HJ, Haug M, Harzer G. Effects of dietary long-chain polyunsaturated fatty acids on the essential fatty acid status of premature infants. Eur J Pediatr 1989;148:669–75.
18. Lauritzen L, Carlson SE. Maternal fatty acid status during pregnancy and lactation and relation to newborn and infant status. Matern Child Nutr 2011;7:Suppl 2:41–58.
19. Marangoni F, Agostoni C, Lammardo AM, Giovannini M, Galli C, Riva E. Polyunsaturated fatty acid concentrations in human hindmilk are stable throughout 12-months of lactation and provide a sustained intake to the infant during exclusive breastfeeding: an Italian study. Br J Nutr 2000;84:103–9.
20. Brenna JT, Varamini B, Jensen RG, Diersen-Schade DA, Boettcher JA, Arterburn LM. Docosahexaenoic and arachidonic acid concentrations in human breast milk worldwide. Am J Clin Nutr 2007;85:1457–64.
21. Yuhas R, Pramuk K, Lien EL. Human milk fatty acid composition from nine countries varies most in DHA. Lipids 2006;41:851–8.
22. Makrides M, Neumann MA, Gibson RA. Effect of maternal docosahexaenoic acid (DHA) supplementation on breast milk composition. Eur J Clin Nutr 1996;50:352–7.
23. Makrides M, Gibson RA, McPhee AJ, et al. Neurodevelopmental outcomes of preterm infants fed high-dose docosahexaenoic acid: a randomized controlled trial. JAMA 2009;301:175–82.
24. Lattka E, Rzehak P, Szabó É, et al. Genetic variants in the *FADS* gene cluster are associated with arachidonic acid concentrations of human breast milk at 1.5 and 6 mo postpartum and influence the course of milk dodecanoic, tetracosenoic, and trans-9-octadecenoic acid concentrations over the duration of lactation. Am J Clin Nutr 2011;93:382–91.
25. van Goor SA, Dijck-Brouwer DA, Hadders-Algra M, et al. Human milk arachidonic acid and docosahexaenoic acid contents increase following supplementation during pregnancy and lactation. Prostaglandins Leukot Essent Fatty Acids 2009;80:65–9.
26. Abbott SK, Else PL, Atkins TA, Hulbert AJ. Fatty acid composition of membrane bilayers: importance of diet polyunsaturated fat balance. Biochim Biophys Acta 2012;1818:1309–17.
27. Hsieh AT, Brenna JT. Dietary docosahexaenoic acid but not arachidonic acid influences central nervous system fatty acid status in baboon neonates. Prostaglandins Leukot Essent Fatty Acids 2009;81:105–10.
28. Neuringer M, Connor WE, Lin DS, Barstad L, Luck S. Biochemical and functional effects of prenatal and postnatal omega 3 fatty acid deficiency on retina and brain in rhesus monkeys. Proc Natl Acad Sci USA 1986;83:4021–5.
29. Carrié I, Clément M, de Javel D, Francès H, Bourre JM. Specific phospholipid fatty acid composition of brain regions in mice. Effects of n-3 polyunsaturated fatty acid deficiency and phospholipid supplementation. J Lipid Res 2000;41:465–72.
30. Farquharson J, Cockburn F, Patrick WA, Jamieson EC, Logan RW. Infant cerebral cortex phospholipid fatty-acid composition and diet. Lancet 1992;340:810–3.
31. Makrides M, Neumann MA, Byard RW, Simmer K, Gibson RA. Fatty acid composition of brain, retina, and erythrocytes in breast- and formula-fed infants. Am J Clin Nutr 1994;60:189–94.

32. Carnielli VP, Simonato M, Verlato G, et al. Synthesis of long-chain polyunsaturated fatty acids in preterm newborns fed formula with long-chain polyunsaturated fatty acids. Am J Clin Nutr 2007;86:1323–30.
33. Carlson SE, Werkman SH, Peeples JM, Cooke RJ, Tolley EA. Arachidonic acid status correlates with first year growth in preterm infants. Proc Natl Acad Sci USA 1993;90:1073–7.
34. Koletzko B, Braun M. Arachidonic acid and early human growth: is there a relation? Ann Nutr Metab 1991;35:128–31.
35. Makrides M, Gibson RA, Udell T, Ried K; International LCPUFA Investigators. Supplementation of infant formula with long-chain polyunsaturated fatty acids does not influence the growth of term infants. Am J Clin Nutr 2005;81:1094–101.
36. Koletzko B, Baker S, Cleghorn G, et al. Global standard for the composition of infant formula: recommendations of an ESPGHAN coordinated international expert group. J Pediatr Gastroenterol Nutr 2005;41:584–99.
37. Birch EE, Hoffman DR, Uauy R, Birch DG, Prestidge C. Visual acuity and the essentiality of docosahexaenoic acid and arachidonic acid in the diet of term infants. Pediatr Res 1998;44:201–9.
38. Auestad N, Montalto MB, Hall RT, et al. Visual acuity, erythrocyte fatty acid composition, and growth in term infants fed formulas with long chain polyunsaturated fatty acids for one year. Ross Pediatric Lipid Study. Pediatr Res 1997;41:1–10.
39. Hørby Jørgensen M, Hølmer G, Lund P, Hernell O, Michaelsen KF. Effect of formula supplemented with docosahexaenoic acid and gamma-linolenic acid on fatty acid status and visual acuity in term infants. J Pediatr Gastroenterol Nutr 1998;26:412–21.
40. Makrides M, Neumann MA, Simmer K, Gibson RA. Erythrocyte fatty acids of term infants fed either breast milk, standard formula, or formula supplemented with long-chain polyunsaturates. Lipids 1995;30:941–8.
41. Simmer K, Patole SK, Rao SC. Long-chain polyunsaturated fatty acid supplementation in infants born at term. Cochrane Database Syst Rev 2011;12:CD000376.
42. Hadders-Algra M. Effect of long-chain polyunsaturated fatty acid supplementation on neurodevelopmental outcome in full-term infants. Nutrients 2010;2:790–804.
43. Delgado-Noguera MF, Calvache JA, Bonfill Cosp X. Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development. Cochrane Database Syst Rev 2010;12:CD007901.
44. Schulzke SM, Patole SK, Simmer K. Long-chain polyunsaturated fatty acid supplementation in preterm infants. Cochrane Database Syst Rev 2011;2:CD000375.
45. The Panel on Dietetic Products Dietetic Products, Nutrition and Allergies on a request from Mead Johnson Nutritionals. Scientific opinion on DHA and ARA and visual development. EFSA J 2009;941:1–14.
46. Hoffman DR, Birch EE, Birch DG, et al. Impact of early dietary intake and blood lipid composition of long-chain polyunsaturated fatty acids on later visual development. J Pediatr Gastroenterol Nutr 2000;31:540–53.
47. Uauy R, Hoffman DR, Mena P, Llanos A, Birch EE. Term infant studies of DHA and ARA supplementation on neurodevelopment: results of randomized controlled trials. J Pediatr 2003;143:Suppl 4:S17–25.
48. Agostoni C, Trojan S, Bellù R, Riva E, Giovannini M. Neurodevelopmental quotient of healthy term infants at 4 months and feeding practice: the role of long-chain polyunsaturated fatty acids. Pediatr Res 1995;38:262–6.
49. Agostoni C, Trojan S, Bellù R, Riva E, Bruzzese MG, Giovannini M. Developmental quotient at 24 months and fatty acid composition of diet in early infancy: a follow up study. Arch Dis Child 1997;76:421–4.
50. Colombo J, Carlson SE, Cheatham CL, Fitzgerald-Gustafson KM, Kepler A, Doty T. Long-chain polyunsaturated fatty acid supplementation in infancy reduces heart rate and positively affects distribution of attention. Pediatr Res 2011;70:406–10.
51. Colombo J, Carlson SE, Cheatham CL, et al. Long-term effects of LCPUFA supplementation on childhood cognitive outcomes. Am J Clin Nutr 2013;98:403–12.
52. Qawasmi A, Landeros-Weisenberger A, Leckman JF, Bloch MH. Meta-analysis of long-chain polyunsaturated fatty acid supplementation of formula and infant cognition. Pediatrics 2012;129:1141–9.
53. Gould JF, Smithers LG, Makrides M. The effect of maternal omega-3 (n-3) LCPUFA supplementation during pregnancy on early childhood cognitive and visual development: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2013;97:531–44.
54. Hageman JH, Hooyenga P, Diersen-Schade DA, Scalabrin DM, Wichers HJ, Birch EE. The impact of dietary long-chain polyunsaturated fatty acids on respiratory illness in infants and children. Curr Allergy Asthma Rep 2012;12:564–73.
55. Xie L, Innis SM. Genetic variants of the *FADS1 FADS2* gene cluster are associated with altered (n-6) and (n-3) essential fatty acids in plasma and erythrocyte phospholipids in women during pregnancy and in breast milk during lactation. J Nutr 2008;138:2222–8.
56. Koletzko B, Lattka E, Zeilinger S, Illig T, Steer C. Genetic variants of the fatty acid desaturase gene cluster predict amounts of red blood cell docosahexaenoic and other polyunsaturated fatty acids in pregnant women: findings from the Avon Longitudinal Study of Parents and Children. Am J Clin Nutr 2011;93:211–9.
57. Steer CD, Hibbeln JR, Golding J, Davey Smith G. Polyunsaturated fatty acid levels in blood during pregnancy, at birth and at 7 years: their associations with two common *FADS2* polymorphisms. Hum Mol Genet 2012;21:1504–12.
58. Lattka E, Koletzko B, Zeilinger S, et al. Umbilical cord PUFA are determined by maternal and child fatty acid desaturase (*FADS*) genetic variants in the Avon Longitudinal Study of Parents and Children (ALSPAC). Br J Nutr 2013;109:1196–210.
59. Morales E, Bustamante M, Gonzalez JR, et al. Genetic variants of the *FADS* gene cluster and *ELOVL* gene family, colostrums LC-PUFA levels, breastfeeding, and child cognition. PLoS ONE 2011;6:e17181.
60. Harsløf LB, Larsen LH, Ritz C, et al. *FADS* genotype and diet are important determinants of DHA status: a cross-sectional study in Danish infants. Am J Clin Nutr 2013;97:1403–10.
61. Schaeffer L, Gohlke H, Müller M, et al. Common genetic variants of the *FADS1 FADS2* gene cluster and their reconstructed haplotypes are associated with the fatty acid composition in phospholipids. Hum Mol Genet 2006;15:1745–56.
62. Mathias RA, Vergara C, Gao L, et al. *FADS* genetic variants and omega-6 polyunsaturated fatty acid metabolism in a homogeneous island population. J Lipid Res 2010;51:2766–74.
63. Bokor S, Dumont J, Spinneker A, et al.; HELENA Study Group. Single nucleotide polymorphisms in the *FADS* gene cluster are associated with delta-5 and delta-6 desaturase activities estimated by serum fatty acid ratios. J Lipid Res 2010;51:2325–33.
64. Jensen HA, Harsløf LB, Nielsen MS, et al. *FADS* single-nucleotide polymorphisms are associated with behavioral outcomes in children, and the effect varies between sexes and is dependent on PPAR genotype. Am J Clin Nutr 2014;100:826–32.
65. Steer CD, Davey Smith G, Emmett PM, Hibbeln JR, Golding J. *FADS2* polymorphisms modify the effect of breastfeeding on child IQ. PLoS ONE 2010;5:e11570.
66. Caspi A, Williams B, Kim-Cohen J, et al. Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. Proc Natl Acad Sci USA 2007;104:18860–5.
67. Martin NW, Benyamin B, Hansell NK, et al. Cognitive function in adolescence: testing for interactions between breast-feeding and *FADS2* polymorphisms. J Am Acad Child Adolesc Psychiatry 2011;50:55–62.e4.
68. Steer CD, Lattka E, Koletzko B, Golding J, Hibbeln JR. Maternal fatty acids in pregnancy, *FADS* polymorphisms, and child intelligence quotient at 8 y of age. Am J Clin Nutr 2013;98:1575–82.
69. Dumont J, Huybrechts I, Spinneker A, et al.; HELENA Study group. *FADS1* genetic variability interacts with dietary a-linolenic acid intake to affect serum non-HDL-cholesterol concentrations in European adolescents. J Nutr 2011;141:1247–53.
70. Standl M, Lattka E, Stach B, et al.; GINIplus Study Group; LISAplus Study Group. *FADS1 FADS2* gene cluster, PUFA intake and blood lipids in children: results from the GINIplus and LISAplus studies. PLoS ONE 2012;7:e37780.

71. Rzehak P, Thijs C, Standl M, et al.; KOALA study group; LISA study group. Variants of the *FADS1 FADS2* gene cluster, blood levels of polyunsaturated fatty acids and eczema in children within the first 2 years of life. PLoS ONE 2010;5:e13261.
72. Standl M, Sausenthaler S, Lattka E, et al.; GINIplus and LISAplus Study Group. *FADS* gene variants modulate the effect of dietary fatty acid intake on allergic diseases in children. Clin Exp Allergy 2011;41:1757–66.
73. Chisaguano AM, Montes R, Pérez-Berezo T, et al. Gene expression of desaturase (*FADS1* and *FADS2*) and Elongase (*ELOVL5*) enzymes in peripheral blood: association with polyunsaturated fatty acid levels and atopic eczema in 4-year-old children. PLoS ONE 2013;8:e78245.
74. Agostoni C, Riva E, Bellù R, Trojan S, Luotti D, Giovannini M. Effects of diet on the lipid and fatty acid status of full-term infants at 4 months. J Am Coll Nutr 1994;13:658–64.
75. Kuipers RS, Luxwolda MF, Sango WS, Kwesigabo G, Dijck-Brouwer DA, Muskiet FA. Maternal DHA equilibrium during pregnancy and lactation is reached at an erythrocyte DHA content of 8 g/100 g fatty acids. J Nutr 2011;141:418–27.
76. Harris WS. The omega-3 index: clinical utility for therapeutic intervention. Curr Cardiol Rep 2010;12:503–8.