Impact of maternal diet on human milk composition and neurological development of infants

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ABSTRACT
Maternal nutrition has little or no effect on many nutrients in human milk; for others, human milk may not be designed as a primary nutritional source for the infant; and for a few, maternal nutrition can lead to substantial variations in human milk quality. Human milk fatty acids are among the nutrients that show extreme sensitivity to maternal nutrition and are implicated in neurological development. Extensive development occurs in the infant brain, with growth from ~350 g at birth to 925 g at 1 y, with this growth including extensive dendritic and axonal arborization. Transfer of n–6 (omega-6) and n–3 (omega-3) fatty acids from the maternal diet into human milk occurs with little interconversion of 18:2n–6 to 20:4n–6 or 18:3n–3 to docosahexaenoic acid (DHA) and little evidence of mammary gland regulation to maintain individual fatty acids constant with varying maternal fatty acid nutrition. DHA has gained attention because of its high concentrations and roles in the brain and retina. Studies addressing DHA intakes by lactating women or human milk amounts of DHA at levels above those typical in the United States and Canada on infant outcomes are inconsistent. However, separating effects of the fatty acid supply in gestation or in the weaning diet from effects on neurodevelopment solely due to human milk fatty acids is complex, particularly when neurodevelopment is assessed after the period of exclusive human milk feeding. Information on infant fatty acid intakes, including milk volume consumed and energy density, will aid in understanding of the human milk fatty acids that best support neurological development. Am J Clin Nutr 2014;99 (suppl):734S–41S.

INTRODUCTION
Recent years have seen a growing appreciation of the importance of promoting and supporting human milk feeding for optimizing infant growth and development, including neurological development. At the same time, the understanding of the substantial morphologic and functional development in the brain, and potential for long-lasting deficits in neurological function because of environmental insults in the 2 y after birth, has increased. Nutrition is clearly a major modifiable environmental factor able to affect neurological development, although robust evidence to support a direct link between maternal nutrition, human milk nutrients, and neurological development in the infant is limited. Maternal nutrition has little or no effect on the amount of many nutrients in human milk; and for others, such as iron and zinc, human milk may not be designed as a primary source. A few nutrients relevant to infant neurological development, however, do vary in human milk as a result of maternal nutrition. These nutrients include the following: vitamin A; several water-soluble vitamins including vitamin B-6, vitamin B-12, and folate; iodine and selenium; and fatty acids. Recent reviews on maternal nutrition and human milk fatty acids because of the considerable differences in human milk fatty acids due to maternal lipid nutrition and the possibility that poor fatty acid nutrition can alter neurological development in breastfed infants. Particular attention is given to the n–3 fatty acids because of the dependence of humans on a dietary source of n–3 fatty acids and the high amounts of DHA (22:6n–3) in the brain and retina. Discussion is focused on infants born at term gestation and does not address the needs of preterm infants or infants with congenital or acquired disease that may alter fatty acid requirements. A brief background on infant neurological development is included to provide context to the consideration of early fatty acid nutrition, as provided by human milk, and neurological development of healthy term gestation infants.

NEUROLOGICAL DEVELOPMENT AND NUTRITIONAL VULNERABILITY
Advances in understanding the impact of early nutritional deficiencies, and by extension developing science-based information on which to set nutrient requirements to support neurological development, are hindered by the complexity of human brain development, ethical and practical limitations of research in infants, and difficulties of separating the effects of the nutrients supplied by human milk from those supplied in gestation and the weaning diet. In general, the concept of nutritional vulnerability during early brain development refers to lasting deficits in neurological function that result from deficiency of

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a dietary nutrient that perturbs normal brain development in such a way that recovery is not achieved, even with later nutritional rehabilitation (8, 9). Examples include the cognitive and behavioral deficits in later life among individuals born preterm and fed formulas designed for term gestation infants rather than human milk or nutrient-enriched preterm formulas (10, 11) or those associated with iron deficiency in infancy (12).

Potential misconceptions regarding brain growth spurts and vulnerable stages of brain development deserve comment. Brain growth curves depicting increments in brain weight relative to body weight indicate rapid brain growth (a spurt) in late gestation with decreasing relative rates of brain growth after birth (13). However, the continuing body weight gain after birth acts to decrease the rate of brain growth when expressed relative to body weight and incorrectly infers slowing of brain growth, rather than highlighting the rapid brain growth that continues throughout the first postnatal year (14) (Figure 1). At term birth, the infant brain weighs an average of 350 g, representing ~10% of body weight, and will almost double in weight to ~660 g by 6 mo of age. By 1 y of age, the infant brain will increase another 40%, to 925 g, at which time it will have reached ~70% of the adult brain weight (~1300–1400 g, 2% of adult body weight) (15, 16).

In addition to substantial structural and functional development, the infant brain is metabolically active and consumes ~50% of resting energy metabolism (17). The large brain relative to body size, rapid anatomic and functional development, and high metabolic activity may confer greater sensitivity of the infant brain compared with the adult brain to deficits in energy and nutrients. Relevant to the discussion, much of the increase in the cerebral cortex in the first year after birth is explained by gray matter rather than white matter (myelination) growth, with much of this considered a result of changes in glia and extensive dendritic and axonal arborization (16, 18). Neural synapses proliferate with rates of up to almost 40,000 synapses formed per second, increasing logarithmically through the first year after birth, with rates of synapse formation peaking at ~8 mo of age (16, 19). These synapses are rich in the n–3 fatty acid DHA, which is known to be important in neurite outgrowth, dendritic complexity, and neurotransmitter metabolism (20). Peak synaptic density in the human prefrontal cortex occurs at ~4–5 y of age (21), with growth and strengthening of neural synapses being a major event in infancy (22). The cell division involved in neurogenesis, on the other hand, is largely prenatal in the human brain and is complete by 20 wk of gestation, with quite similar cortical neuron numbers in the infant at birth and at 1 and 2 y of age (14, 16).

Cortical neuroplasticity, which is key to learning and memory, was recently shown to be reduced in children born preterm (23). Whether nutrient deficiencies affect the connectivity rearrangements and enhanced synapse turnover involved in learning (24) is not known. However, isolation of the effects of human milk fatty acids on neurodevelopment of the breastfed infant is complicated by possible recovery/compensation, exacerbation, or emergence of deficits affecting neural function with introduction of complementary foods into the infant’s diet. This concept is shown in Figure 1, which depicts brain growth in grams during human milk feeding from birth to 4 mo or 6 mo of age, and the substantial continuing growth from 4 or 6 mo to 24 mo of age. Apropos to this discussion are the recent demonstrations of increased cortical activation during sustained attention in 8- to 10-y-old boys given a short 8-wk supplementation with 400 or 1200 mg DHA/d (25) and decreased reaction times in memory tasks in adults given 1200 mg DHA/d for 6 mo (26). Studies such as the latter (25, 26) suggest that recent fatty acid nutrition affects neurological function and may be important throughout the life span. In summary, considerable brain growth occurs throughout the first year after birth, with extensive structural and functional expansion of neural networks. Adequate supplies of energy and

FIGURE 1. Brain growth from conception to 24 mo of age with a representation of the amount of brain growth during exclusive breastfeeding or after complementary foods have been added to the infant diet. The stacked columns show the increase in brain weight from conception to birth, then during exclusive breastfeeding to age 6 mo (left panel) or 4 mo (right panel), with brain weight gain after the introduction of complementary foods from 6 or 4 mo to 12 mo of age, then to 24 mo of age.
fatty acids required for synthesis, functionality, and protection of neural membrane can reasonably be considered fundamental to optimizing neurological development.

MATERNAL NUTRITION AND HUMAN MILK FATTY ACIDS

Human milk contains substantial amounts of lipids, which are present as globules composed of a core of nonpolar lipids, including triglycerides, cholesterol esters, retinyl esters, and other lipophylic nutrients, surrounded by the milk fat globule membrane. Human milk lipid concentrations vary widely from ~2 to 6 g/dL, and this variability appears to be largely independent of maternal nutrition (1, 2, 27). Approximately 98% of the lipids in human milk consists of triglycerides, each containing 3 fatty acids of which most are sensitive to maternal nutrition. Because triglycerides are the single most important source of energy in human milk, their highly variable concentration has broad implications for the energy density (kcal/100 mL), protein and essential nutrient:energy ratio, proportion of energy from fat and carbohydrate, and concentration of specific fatty acids. The widely variable total 24-h milk volume, reported as 440–1220 g/d, produced by different women (28) also has significant implications for estimating fatty acid intakes of the breastfed infant.

Human milk fatty acids are derived from endogenous synthesis in the mammary gland and uptake from maternal plasma. Both mammary gland fatty acid synthesis and the fatty acids available for uptake from the maternal plasma are influenced by maternal nutrition (27, 29–33). Much of the data on human milk fatty acids, however, are expressed as relative fatty acid percentages, without information on the amount of fat or energy density of the milk or milk volume consumed by the infant. As a result, estimation of fatty acid intakes in breastfed infants is reduced to extrapolations based on an assumption of an average volume of milk consumed and an average milk fat content. Because each triglyceride has a finite 3 fatty acids, human milk fatty acids are mutually dependent, with an increase in any one fatty acid of necessity requiring a decrease in one or more other fatty acids. Few studies to date on human milk fatty acids have considered fatty acid balance or the extent to which diet-induced increases in specific fatty acids alter the content of other fatty acids.

An extensive body of literature on human milk fatty acids from different countries and after manipulation of maternal lipid nutrition has been published (27, 29–33). These studies uniformly show that many of the fatty acids in human milk, including monounsaturated, n–6, and n–3 fatty acids, vary widely depending on maternal lipid nutrition. In seminal studies in the 1950s, Insull et al. (34) provided lactating women with 40% of dietary energy from lard, corn oil, or linseed oil. Within 2–3 d of changing from the usual diet to 40% corn oil (containing ~52% of 18:2n–6), the amounts of 18:2n–6 increased from 8–10% to ~42% of the milk fatty acids. At the same time, arachidonic acid (20:4n–6) decreased from 0.7% to 0.3% and DHA decreased from 0.3% to trace amounts in the mothers’ milk. The authors concluded that dietary fatty acids are rapidly transferred into milk and that within 2 or 3 d the character of human milk fat can be radically changed to mimic the dietary fat (34). Since that time, numerous articles have described population differences in human milk fatty acids and dietary interventions that combine to give robust evidence that maternal lipid nutrition is the single most important factor contributing to the variability in human milk fatty acids (27, 29–33).

Human milk has 4–27% medium-chain fatty acids (MCFA), mostly 10:0, 12:0, and 14:0, which are synthesized in the mammary gland. MCFA synthesis is elevated in lactating women with high-carbohydrate, low-fat diets and low plasma triglycerides (27, 35). Current information suggests that mammary gland fatty acid synthesis is regulated inversely with uptake of fatty acids from plasma, thus enabling maintenance of triglyceride secretion into human milk, regardless of the maternal dietary fat and carbohydrate intake (35). After absorption, MCFA undergo rapid β-oxidation, providing a dose-dependent increase in infant plasma ketones (36). Ketones are an important source of energy and acetyl-CoA for the developing brain, with switches in energy substrate transport into the brain during development. High expression of the monocarboxylic acid (ketone) transporter at the brain-blood barrier occurs during milk feeding, with a decline on weaning (37–39). Plasma ketones are also higher in term gestation breastfed infants than in infants fed formula (40, 41). Whether the wide variation in human milk MCFA, varying from ~2% to 10% of breastfed infants’ energy intake, has relevance to infant neurological development is not known. However, high MCFA amounts in human milk are accompanied by lower MUFA, 18:2n–6, and 18:3n–3 (35).

trans Fatty acids consumed in hydrogenated vegetable oils were as high as 12–18% of human milk fatty acids in the United States and Canada before approximately 2002 but have since decreased (42–44). Experimental studies implicated exposure to high maternal trans fatty acids in altered behavior in rodents (45, 46), but no such data exist for human infants. However, human milk with high trans fatty acids has lower n–6 and n–3 fatty acids, including 18:2n–6, 18:3n–3, 20:4n–6, and DHA (42, 47), possibly explained by poorer diet fat quality in women with high intakes of foods containing hydrogenated oils.

Because humans are unable to synthesize n–6 or n–3 fatty acids, all of the n–6 and n–3 fatty acids secreted into human milk and accumulated in infant tissues during exclusive human milk feeding must be derived from the maternal diet. Because the n–6 and n–3 fatty acids are unevenly distributed in foods, and n–6 and n–3 fatty acid secretion into human milk does not appear to be regulated by the mammary gland (33), differences in maternal n–6 and n–3 fatty acid nutrition during lactation can result in large differences in n–6 and n–3 fatty acids in human milk (27–33). The average and range of different n–6 and n–3 fatty acids in human milk from 2 representative studies in Canada and the United States are shown in Table 1 (35, 43). Whereas it can be seen that collapsing the data to consider only group averages suggests very similar fatty acid amounts, variability between individual women is high, with 18:2n–6 varying from ~7% to 26% and DHA varying >10-fold from <0.1% to >1% of fatty acids (Table 1). The 18-carbon chain fatty acids 18:2n–6 and α-linolenic acid (18:3n–3) are synthesized in plant cells and passed up the food chain to animals. However, the major source of 18:2n–6 and 18:3n–3 in many diets is vegetable

Abbreviations used: FADS, fatty acid desaturase; MCFA, medium-chain fatty acid; MDI, mental developmental index; PDI, psychomotor development index.
Human consumption (48, 49) may be seen from studies on the prepared foods, and changes in feeding of livestock destined for has shifted because of use of refined vegetable oils, processed and acids reflect the fatty acid quality of the lactating mother's diet 30–50 y (31, 34) emphasizes that human milk unsaturated fatty acids in human milk in westernized countries, including the United States, Canada, and the United Kingdom, over the past increase in 18:2n–6 from mean levels of 6–7% to 13–18% fatty, 0.3% fatty acids (30, 35, 42–44, 51, 53) (Table 1). The 100% the United States and Canada have milk DHA amounts of, although DHA/d achieve human milk levels of 0.3–0.35% DHA (27–33). Extrapolation from dietary and supplementation studies suggests that intakes of ~300 mg DHA/d achieve human milk levels of 0.3–0.35% DHA (27–33, 51, 52), although >50% of women in studies on human milk in the United States and Canada have milk DHA amounts of <0.3% fatty acids (30, 35, 42–44, 51, 53) (Table 1). The 100% increase in 18:2n–6 from mean levels of 6–7% to 13–18% fatty acids in human milk in westernized countries, including the United States, Canada, and the United Kingdom, over the past 30–50 y (31, 34) emphasizes that human milk unsaturated fatty acids reflect the fatty acid quality of the lactating mother’s diet and that dependence on maternal nutrition is not unique to DHA. Insight into how far the fatty acid composition of human milk has shifted because of use of refined vegetable oils, processed and prepared foods, and changes in feeding of livestock destined for human consumption (48, 49) may be seen from studies on the milk fatty acids in lactating Bolivian women consuming forager-horticulturalist diets and with only 2% of dietary energy from purchased foods (53). Milk from these women compared with US women had 50% lower 18:2n–6 (9.31% compared with 18.09%) and >3-fold higher DHA (0.62% compared with 0.13%) (Table 1). In summary, the direct dependence of human milk unsaturated fatty acids, including 18:2n–6, 18:3n–3, and DHA, on maternal nutrition positions human milk as a biological biomarker of the fatty acid quality of the lactating mother’s diet. Whether the range of fatty acids in human milk meets the needs of the breastfed infant, and for how long after birth, is a different question and one that requires evidence based on infant outcome.

### HUMAN MILK FATTY ACIDS AND INFANT NEUROLOGICAL DEVELOPMENT

Much of the work on infant fatty acid nutrition in recent decades has been dominated by questions on the amounts of n–3 fatty acids needed by the infant brain and retina. Approximately 10% of human brain fatty acids consist of DHA, with amounts reaching as high as 35% DHA in the fatty acids in ethanolamine and serine-containing phospholipids of neural synapses (20). DHA is also high in the retinal photoreceptor outer segments where it functions in visual signal transduction (54, 55). After birth, the amount of DHA in the brain continues to increase to age 2 y and beyond, explained by the increase in brain weight. DHA is present in the brain together with high amounts of 20:4n–6 and 22:4n–6, although the brain has very low amounts of 18:2n–6, 18:3n–3, and 20:5n–3 (20, 56). More than 50% of the human infant brain fatty acids are saturated, with 20–25% MUFAs, and 25–30% n–6 and n–3 fatty acids, with little change in the relative proportions of different fatty acids between birth and 5 y (56). Although the growing infant brain accumulates SFAs and MUFAs, there is no information to suggest that human milk fatty acids influence SFA and MUFA accretion in the infant brain.

Early studies on the essentiality of n–3 fatty acids began with work in rodents, followed by nonhuman primates that showed neurological and visual function deficits in animals fed safflower

### TABLE 1

Major n–6 and n–3 fatty acids in human maternal milk show the wide individual variability in fatty acid levels and the impact of traditional and modern diets.

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>United States (^2) ((n = 81))</th>
<th>Canada (^3) ((n = 149))</th>
<th>United States (^4) ((n = 35))</th>
<th>Traditional diet; Bolivia (^4) ((n = 35))</th>
</tr>
</thead>
<tbody>
<tr>
<td>n–6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18:2n–6</td>
<td>12.7 (8.1–21.7)</td>
<td>13.6 (7.2–26.2)</td>
<td>18.1 (12.8–24.1)</td>
<td>9.31 (3.86–14.8)</td>
</tr>
<tr>
<td>20:3n–6</td>
<td>NR</td>
<td>0.31 (0.14–0.60)</td>
<td>0.33 (0.23–0.43)</td>
<td>0.44 (0.29–0.59)</td>
</tr>
<tr>
<td>20:4n–6</td>
<td>0.47 (0.25–0.70)</td>
<td>0.36 (0.10–0.64)</td>
<td>0.56 (0.43–0.69)</td>
<td>0.96 (0.44–1.48)</td>
</tr>
<tr>
<td>n–3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18:3n–3</td>
<td>0.95 (0.54–1.70)</td>
<td>1.60 (0.68–3.18)</td>
<td>1.39 (0.61–2.17)</td>
<td>1.64 (0.60–2.68)</td>
</tr>
<tr>
<td>20:5n–3</td>
<td>0.02 (0.00–0.22)</td>
<td>0.08 (0.02–0.45)</td>
<td>0.06 (0.02–0.10)</td>
<td>1.17 (0.04–0.30)</td>
</tr>
<tr>
<td>22:5n–3</td>
<td>0.10 (0.05–0.41)</td>
<td>0.12 (0.04–0.52)</td>
<td>0.14 (0.11–0.17)</td>
<td>0.36 (0.53–1.06)</td>
</tr>
<tr>
<td>22:6n–3</td>
<td>0.23 (0.07–1.20)</td>
<td>0.21 (0.03–1.13)</td>
<td>0.13 (0.04–0.21)</td>
<td>0.62 (0.31–0.93)</td>
</tr>
</tbody>
</table>

\(^1\) All values are percentages of fatty acids in total milk fatty acids. NR, not reported.  
\(^2\) Values are means (ranges) from Innis and King (42).  
\(^3\) Values are means (ranges) from Mosley et al (43).  
\(^4\) Values are means (IQRs) for US women and women in Bolivia consuming a traditional forager-horticulturalist diet (adapted from reference 53).
(<0.2% 18:3n–3) rather than soybean (6–8% 18:3n–3) oil as the only fat source (57). The loss of DHA from the brain and retina was accompanied by increased 22:4n–6 and 22:5n–6, and these observations have been repeated and confirmed in numerous studies with animals fed diets limited in n–3 fatty acids (57). Autopsy studies, performed before the addition of DHA and 20:4n–6 to infant formula, showed lower DHA and higher 22:4n–6 and 22:5n–6 in the brains of human infants who before death were fed formula compared with the brains of infants who had been breastfed (58, 59). Accumulation of 22:5n–6 and 22:4n–6 and 22:5n–6 in the brains of human infants who before death were fed formula compared with the brains of infants who had been breastfed (58, 59). Accumulation of 22:5n–6 and 22:4n–6, which are synthesized from 18:2n–6, is inconsistent with a theory that low Δ^5 and/or Δ^6 fatty acid desaturase (FADS) activity limits infants’ ability to form DHA, unless some aspect of n–3 FADS and elongation not shared by the n–6 fatty acids is involved. Regardless, experimental studies have shown that DHA from the maternal diet is transferred to the fetal and infant brain and is more efficient as a source of neural tissue DHA than an equivalent amount of 18:3n–3 (60, 61). From this perspective, a dietary source of DHA is expected to reduce the risk of neural tissue DHA insufficiency. In contrast to DHA, human infant autopsy data yield no evidence that the brain requires a dietary source of 20:4n–6, because 20:4n–6 was at least as high in the brain and retina of infants fed formula devoid of 20:4n–6 as in breastfed infants (58, 59). Before birth, nutrients are transferred from the mother to enable growth and development of organs, with accumulation of adipose tissue and storage of nutrients that contribute to nutritional adequacy over the first month of life. Although placental fatty acid transfer increases to only ~11% of fetal energy requirements by term gestation (62), the human infant at birth is 10–13% body fat, and one of the fattest known newborn animals (63). Recent studies estimated that an average of 68%, 44%, and 50% of total body 18:2n–6, 20:4n–6, and DHA, respectively, is present in the adipose tissues of term gestation infants at birth (64). Fetal n–6 and n–3 fatty acid nutrition is modified by maternal diet, with a direct positive correlation between maternal and fetal plasma n–6 and n–3 fatty acids, including 18:2n–6, 18:3n–3, DHA, and trans fatty acids (65). With regard to human milk, women with higher intakes of DHA give birth to infants with higher blood concentrations of DHA (31). The extent to which the maternal fatty acid supply in gestation determines fetal adipose fatty acid quality and whether adipose tissue fatty acids are available to support infant neural tissue growth in the first month after birth are unclear. Adipose tissue DHA and 20:4n–6 decrease, whereas 18:2n–6 and 18:3n–3 increase in breastfed infants after birth, with a greater decrease in adipose tissue DHA and an increase in 18:2n–6 and 18:3n–3 in infants fed formula rather than breastfed (66). However, the expansion of adipose tissue using fatty acids from human milk or formula, rather than loss of DHA to support growth of other tissues, could explain these findings. As introduced, foods vary widely in fatty acid composition, with most cereals, fruit, and vegetables being low in fat and n–6 and n–3 fatty acids, whereas animal-derived foods provide variable DHA. As in the adult diet, the complementary foods added to breastfed infants’ diets can dilute, maintain, or increase the intake of specific fatty acids relative to total energy intake and body weight. For example, introduction of animal protein and sources of heme iron, such as meats, fish, poultry, and egg yolk, from ~6 mo of age, as recommended in Canada (67), provides DHA, whereas the addition of cereals from 4 mo followed by vegetables and fruit decreases the intakes of all n–6 and n–3 fatty acids per kilocalorie and kilogram of body weight. In summary, the requirements for particular fatty acids from human milk to support infant neurological development involve consideration of the infant’s fatty acid status at birth and the age at which complementary foods are given and what those foods are. Several observation studies have reported a positive relation between visual and neurodevelopment in term gestation breastfed infants and DHA amounts in their mothers’ milk (68–71), although many factors could explain this association. Several clinical studies have also addressed the effect of adding DHA, usually with 20:4n–6, to infant formula on neurological and visual function development of formula-fed infants, and reviews are available (71, 72). Recent studies in this field showed benefits to visual function and attention in term gestation infants in the United States who were fed formula with 0.32% DHA throughout the first year after birth, with no additional benefit of 0.64% or 0.96% DHA (73, 74). Whereas DHA is beneficial in formula fed throughout the first year, numerous differences in formula vegetable oil fatty acids, the absence of the milk fat globule membrane, and lower plasma LDL and HDL concentrations in formula-fed compared with breast-fed infants (75) suggest caution in extrapolating dietary fatty acid requirements from infants fed formula to those fed human milk. The effects of increasing human milk DHA through maternal supplementation on infant neurological development have been assessed in a few studies with null, positive, and negative effects on term gestation infants (71, 76). Jensen et al (51) randomly assigned lactating women in the United States to receive a placebo or 200 mg DHA/d until 4 mo postpartum, and this gave human milk levels of DHA of 0.2% and 0.35% fatty acids, respectively. Infant visual acuity and neurodevelopment at 12 mo or 30 mo of age were not different with the exception of a higher mental developmental index (MDI) but not psychomotor development index (PDI) at 30 mo in infants of mothers given DHA. Follow-up of the infants at 5 y of age showed better sustained attention but no other neuropsychological or visual system differences in children who had been breastfed by mothers given DHA (77). A dose-dependent increase in human milk DHA from 0.1% to 1.17% of fatty acids over the first 3 mo postpartum in Australia was associated with higher infant MDI but not PDI at 12 mo, with no effect on MDI or PDI at 24 mo, or visual acuity at any age (52). In Denmark, lactating women were randomly assigned to receive 4.5 g fish oil/d (900 mg DHA) or olive oil for the first 4 mo after delivery, which provided human milk with 1.3% or 0.4% DHA, respectively, and visual acuity and neuropsychological and physical development of the children were assessed (78–81). Visual acuity at 4 mo of age was not altered by increasing breast milk DHA to 1.3% of milk fatty acids (79). In children who were breastfed by the mothers given fish oil, problem-solving was higher in infant girls, but not boys, and language development was lower in 1- and 2-y-old boys compared with girls and boys of mothers given olive oil (80). Although increasing the mothers’ milk DHA had no effect on child mean performance at 7 y of age on tasks of working memory, speed of processing, or inhibitory control, boys who were breastfed by mothers given fish oil had poorer prosocial behavior and higher blood pressure and energy intake compared
with boys in the olive oil placebo group (78, 81). In Norway, Helland et al (82, 83) gave women cod liver oil (1.183 mg DHA/d) or corn oil from 17–19 wk of gestation until 3 mo after delivery, and this provided human milk with a mean DHA (−1 to +1 SD) of 1.26% (0.77–1.75%) and 0.47% (0.20–0.74%) in the 2 groups, respectively, at 3 mo postpartum. Whereas there were no effects on infant novelty preference at 6 or 9 mo of age (82), follow-up at 4 y of age found significantly higher mean mental composite test scores in infants of mothers given cod liver oil rather than corn oil (106.4 ± 7.4 compared with 102.3 ± 11.3 in n = 48 and 36 infants, respectively; P = 0.049), with no effect evident at 7 y of age (83, 84). The studies described used different doses and sources of DHA, altering human milk DHA in different amounts and for different durations for up to 4 mo after birth, with different background maternal diets, unknown effects of the weaning diet, and different measures of infant and child development given after cessation of the intervention while brain growth was continuing (Figure 1). Given the wide variability in human milk volume and fat content (27, 28), knowledge of DHA intakes in terms of mg/d and mg/kcal among breastfed infants may lead to better understanding of the threshold of DHA intake among young infants below which neurological development is compromised. Attention also needs to be given to the possibility that supplementation of lactating mothers with n–3 fatty acid–rich oils may have a threshold above which there are untoward effects on infant and child development. The contribution of fish to other key nutrients such as iodine, which are critically important for infant neurological development (5, 85), may also contribute to inconsistency between studies addressing the importance of maternal fish and seafood intake during pregnancy and lactation and intervention trials with n–3 fatty acid–rich oils.

Genetic variation (single nucleotide polymorphisms) in FADSs and elongases needed to convert 18:2n–6 to 20:4n–6 and 18:3n–3 via 20:5n–3 to DHA are associated with differences in blood lipid n–6 and n–3 fatty acids (86, 87). In general, variability due to genetic variation is greatest for 20:4n–6, with much smaller effects on 20:5n–3 and DHA (86–88). Genetic variants of FADSs are also associated with variability in human milk 20:4n–6, as well as 20:5n–3 and DHA (89, 90). Unexpectedly, minor allele variants in FADS2, which encodes Δ⁶-desaturase, also seem to be associated with a blunted increase in mothers’ transfer of DHA from fish into milk (90). Reasonably, infant genetic variation could also affect requirements of the breastfed infant for particular fatty acids from human milk. However, recent studies found no effect of child FADS genotype on intelligence quotient among children who had been breastfed as infants, although genetic variation in FADSs and genes encoding fatty acid elongation was associated with cognitive development in children who were not breastfed (91, 92).

CONCLUSIONS

Substantial structural and functional development occurs in the brain between birth and 1 y of age, and this involves accumulation of SFAs and MUFA s, 20:4n–6, 22:4n–6, and DHA. Human milk is often used as the basis from which to derive nutrient requirements for infants from 0 to 6 mo and 7–12 mo of age, but human milk fatty acids reflect maternal fatty acid nutrition with no clear indication that their quality or quantity is regulated by the mammary gland to meet infant fatty acid needs. Comparative data over time and from different populations provide evidence that human milk fatty acids have shifted with modern food supplies and dietary practices, raising the possibility that maternal lipid nutrition during lactation may, in some cases, lead to human milk fatty acid compositions that fail to best support infant neurological development. Maternal genetic variation may also contribute to variation in human milk fatty acids, although the effect size is generally much smaller than that of the maternal dietary fat composition. DHA, but not 20:4n–6, is lower in the brain of infants fed formula with no DHA or 20:4n–6 than in breastfed infants, raising the possibility that variability in human milk DHA will alter infant neurological development. A limited number of studies have assessed the effects of maternal intake and human milk amounts of DHA higher than those typical of women in the United States and Canada, making conclusions difficult. These studies have generated evidence of null, adverse, and positive effects on infant and child development. Although evidence that human milk fatty acid quality can alter infant neurological development is available, it is possible that n–3 fatty acid–rich oil supplements may not have the same implications for human milk quality and the breastfed infant as a maternal diet in which part of the protein is provided by fish and other seafoods.

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