Nutritional Factors in Fetal and Infant Brain Development

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Key Messages

- Maternal nutrition is integral to fetal and, if breastfeeding, infant brain development.
- Nutrition effects are governed by the timing, severity, and duration of a deficiency or a sufficiency.
- Genetics and epigenetics determine the individual needs for and metabolism of nutrients.
- Nutrients work together in a synergistic manner for the benefit of the organism.

Keywords

Brain development · Fetal nutrition · Infant nutrition · Maternal nutrition

Abstract

Fetal and infant brain development determine the trajectory of the organism across the lifespan. Optimal maternal and infant nutrition during the period of rapid brain development is vital to the integrity of the neural substrate for subsequent lifelong functions. The goal of this review is to educate the

reader on the effects of fetal and infant nutrition on the developing human brain. A review of the literature reveals 6 nutrients that have been studied with respect to maternal nutrition and subsequent offspring brain development: folate, iodine, iron, vitamin D, choline, and docosahexaenoic acid (DHA; 22:6n-3). The research is discussed with a focus on the timing of nutrient needs (preconception, prenatally, and postnatally) as well as potential confounding and unobserved variables.

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Introduction

Arguably one of the most important organs in the body, the brain requires a high level of nutrition to function optimally. In fact, glucose utilization is 60% of the total in the body. During development, proper maternal and infant nutrition are needed to ensure that the neural substrates are laid down with integrity. As detailed elsewhere [1], the sequelae of nutrient deficiencies depend on timing, dose, and duration: at what point in development did the deficiency occur; how severe was it; and how long did it last? Each nutrient has its own period when its lack can cause developmental issues; this period is

Table 1. Examples of natural sources of select nutrients

Nutrient	Examples of sources
Folate	Dark leafy greens Legumes Dairy products Grains Poultry Eggs
Iodine	Seaweed Seafood Oysters Legumes Strawberries Iodized salt
Vitamin D	Sunshine Fatty fish Beef liver Egg yolks Mushrooms
Iron	Red meat Spinach Liver Shellfish Legumes
Docosahexaenoic acid	Free-range eggs Grass-fed beef Fatty fish Algae
Choline	Eggs Red meat Liver Peanuts Dark leafy greens

known as a sensitive period. That is, the organism is especially sensitive to a deficiency of a specific nutrient at a specific time. If the deficiency is severe and long lasting, the issues can be devastating and irreversible. In this review, the known important aspects of maternal and infant nutrition that contribute to brain development and function will be discussed. It should be noted that maternal nutrition is integral to other important aspects of human development, such as length of gestation, intrauterine growth restriction, and other birth outcomes that will not be covered here. The goal of this review is to educate the reader on the effects of fetal and infant nutrition on the developing human brain.

A review of the literature reveals 6 nutrients that have been studied with respect to maternal nutrition and subsequent offspring brain development: folate, iodine, iron, vitamin D,

choline, and docosahexaenoic acid (DHA; 22:6n-3). See Table 1 for example sources of these nutrients. The research surrounding these nutrients will be summarized here, as will a few underlying concepts, but the coverage will not be exhaustive.

Importance of Maternal Nutrition before Conception

Women of child-bearing age who are sexually active should be aware that nutrition is important *before* conception. As mentioned, timing is imperative. In the first few weeks of gestation when most women do not know that they are pregnant, the zygote is growing at an incredible rate. Proper nutrition supports the rapid cell division, development of supporting structures such as the placenta, implantation, and neural tube closure that occur in those first few weeks. Therefore, it is important for women of child-bearing age to have the proper nutrients on board in the event of unanticipated pregnancy. Research foci in preconception nutritional needs were suggested by developmental issues. In particular, work has been done to document the effects of folate in the prevention of issues during neurulation and iodine in the prevention of cretinism.

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Folate

The prevalence of neural tube defects (NTD) is 1–10 per 1,000 live births with a higher prevalence in nonviable pregnancies [2]. The severity of effects ranges from anencephaly, which is usually fatal, to asymptomatic closed spinal lesions. In 1964, it was proposed that folate might be involved [3], in part, due to the higher prevalence in low-income, potentially undernourished populations. Supplementation with a multivitamin containing folic acid starting 28 days before conception proved to lower the incidence of NTD relative to the unsupplemented control group [4], and similarly, recurrence was significantly diminished with preconception supplements [5]. Importantly, when classifying women by the quality of their diets, only those with inadequate diets gave birth to infants

Fig. 1. Data from Shaw et al. [7] on the risk of giving birth to an infant with neural tube disorders when preconception dietary intake is in the highest quartile for folate, folate with choline, choline with methionine, choline with betaine, and choline with methionine and betaine.

with NTD [6]. Based on the growing body of evidence, policy makers established a requirement for folic acid in women of child-bearing age, and in the United States, folic acid was added to the food supply in 1998. New evidence suggests that folate may not be the primary B vitamin in the amelioration of NTD [7]. Data collected by Shaw et al. [7] suggest that the risk of NTD is furthest reduced by a high preconception intake of methionine, choline, and betaine in combination rather than intake of folate alone (Fig. 1). Thus, although folic acid supplementation has reduced the incidence of NTD, overall optimal nutrition is important before conception.

Iodine

A major cause of childhood cognitive issues worldwide is maternal iodine deficiency. Iodine is essential (meaning that it needs to be acquired from the diet) and is used in the production of thyroid hormones. During pregnancy, iodine requirements increase because there is an increased need for thyroid hormones (the fetal thyroid does not start working until the second trimester), for transfer of maternal iodine to the fetus throughout gestation, and for renal clearance of iodine. If a woman is severely deficient in the first few days or weeks of gestation, the result is cretinism in the child, which is characterized by mental deficiencies, deaf mutism, and motor spasms of the arms and legs. The severity of the problem is dependent on the severity of the deficiency. It is thought that cretinism is due to the inability of the mother to produce enough thyroid hormone in those crucial first few weeks when the fetal thyroid is not yet functioning. Because thyroid hormones are involved in neurogenesis and neuronal migration as well as several other neuronal processes, the effects of iodine deficiency can be globally pervasive in the brain.

Several iodine supplementation studies have been implemented in developing countries. In a study in Ecuador, one village was treated with iodine and another acted as a control. Mean IQs of the children born in the treated village were higher relative to the control village, but interestingly, if the treatment occurred before pregnancy or in the 1st trimester, the difference in IQ was a full 11 points [8]. Scientists working in New Guinea gave injections of saline or iodine [9]. The untreated group had a cretinism rate of 9% and the treated group had a rate of just 2%. Analyses showed that 6 of the 7 cretins in the treated group were born to mothers who were treated late in pregnancy. So, treatment must be done early in pregnancy, and since most women do not know that they are pregnant in the first few weeks, it is imperative that iodine sufficiency is achieved *before* conception. Salt iodization programs are in place globally, but due to the cost of iodized salt, results have not been as pervasive as expected.

Summary

Folate and iodine are the quintessential examples of the need for good maternal nutrition before conception. Most likely, other nutrients will be found to have just as many profound effects. Thus, women of child-bearing age who are sexually active should be counseled to establish healthy dietary habits such that their nutrition levels are stable and optimal. Importantly, folate and iodine are needed throughout gestation. The next section details other nutrients that have been researched for their utility in fetal development.

Importance of Maternal Nutrition during Gestation

Fetal neural development is dependent on the nutritional environment in utero. A fetus developing in a suboptimal environment will compensate by adapting metabolic systems to the anticipated external world. This adaptation is known as “fetal programming” and is thought to be partially responsible for the progression of disease into adulthood [10]. For example, maternal obesity during gestation has been related to insulin resistance and, thus, metabolic disorder in adulthood [11]. Even though a complete review of the developmental origins of health and disease (DOHaD) hypothesis is beyond the scope of this paper, the concept is important to its thesis: early nutritional programming effectively prepares the fetus and infant for the world to come based on a prediction of the nutrients that will be available. The seminal example comes from the Dutch famine of 1944. Offspring of women who were pregnant during the famine and, thus, were unable to provide sufficient nutrients to their fetuses in utero went on

as adults to develop significantly higher levels of cardiovascular disease, obesity, and adult-onset diabetes relative to offspring of mothers who were sufficiently nourished during pregnancy [12]. Fetal programming in this example would have prepared the fetus epigenetically for a world with little nutrition. Then, with the famine resolved, the previously famine-programmed child would have had access to plentiful food, and the system would have experienced a mismatch between prenatal and postnatal nutrition environment. DOHaD predicts that this mismatch can result in a progression to disease. Thus, maternal nutrition can have a profound and long-lasting effect on the developing fetus. In what follows, the importance of maternal vitamin D, iron, DHA, and choline will be detailed.

Vitamin D

Maternal vitamin D deficiency has been studied extensively for its effect on the developing fetal brain as those born in winter have a higher risk of developing schizophrenia [e.g., 13]. The fetus is wholly dependent on maternal provision of vitamin D [14]. When the mother is deficient, the fetus is deficient. Scientists utilizing animal models revealed that vitamin D deficiency results in morphologically different brains in the offspring: vitamin D has a role in brain size, ventricle size, cell proliferation, and growth factor signaling [15]. To date, all the research in humans has been correlational; it would not be ethical to randomize women to remain deficient throughout pregnancy.

Effects of maternal vitamin D deficiency on IQ have been mixed. Whereas better scores at 7 years of age on the Wechsler Intelligence Scale for Children (WISC) were related to better maternal vitamin D status and cord blood vitamin D [16], better vitamin D status during pregnancy did not predict better scores on the Kaufman Brief Intelligence Test (KBIT) at 5 years of age [17] or on the Wechsler Abbreviated Scale of Intelligence (WABI) at 9 years of age [18]. Better gestational vitamin D status has been related to better language abilities at 5 and 10 years of age [19]. In one of the few studies wherein toddler development was assessed, researchers reported a relation between both the psychomotor and mental subscales of the Bayley Scales of Infant Development (BSID): higher vitamin D status at week 13.5 of gestation was related to higher BSID scores in 14-month-olds [20]. Finally, maternal vitamin D status has been related to risk of attention deficit hyperactivity disorder (ADHD) with lower maternal vitamin D predicting higher risk of the child developing ADHD [21].

Certainly, the body of research suffers from a lack of consistency in assessments and study timepoints, as is often the case in epidemiological analyses of established datasets. In addition, and perhaps more importantly, women who are vi-

tamin D deficient generally are of lower socioeconomic status, and as such, would be more susceptible to viruses, more likely to be consuming teratogenic substances (e.g., tobacco and alcohol), and would be more likely to be undernourished in general.

Iron

Iron deficiency is the number one nutrition issue in the world. The sequelae of iron deficiency result in a loss of billions in productivity annually. One can be iron deficient without being anemic, but iron deficiency with anemia (IDA) rates can be quite high – as high as 77.2% among children 1–3 years of age in rural India [22]. In the USA, the prevalence of iron deficiency in those 1–2 years of age is as high as 30.5% based on total body stores [23]. Finally, rates of deficiency among pregnant women worldwide reach as high as 50% [24]. Iron deficiency prenatally and in infancy can cause irreversible neural issues. Moreover, maternal hypertension and smoking during pregnancy are known to cause a decrease in materno-fetal transport of iron, and gestational diabetes results in a higher fetal need for iron. Thus, pathways to iron deficiency vary, and it is not known if supplementation can prevent subsequent neurobehavioral issues in the offspring.

Fetal iron sufficiency supports neural energy metabolism, the development of dendrites and synapses, the synthesis of neurotransmitters, and the onset of myelination [25]. As mentioned previously, timing, dose, and duration of the insufficiency determine the sequelae. In an analysis of over half a million of children in Sweden, it was shown that children of mothers who were diagnosed with anemia in the first 30 weeks of pregnancy had a higher incidence of autism spectrum disorder, ADHD, and intellectual disability relative to children of mothers who were diagnosed later in pregnancy or not diagnosed [26]. Thus, the earlier timing and longer duration of the insufficiency led to more severe and diagnosable issues.

Fetal iron needs increase in pregnancies complicated by gestational diabetes. A sample of infants of diabetic mothers (IDM) were followed longitudinally by a research group led by Nelson and Georgieff. These infants were first tested at 38–42 weeks' postmenstrual age in an electrophysiology paradigm known as event-related potentials or ERP to assess their ability to recognize their own mothers' voices [27]. The infants were divided into 2 groups defined as ferritin levels in cord serum above and below 34 µg/L. Neonates in the low-iron group were not able to differentiate their mothers' voices from strangers' voices, whereas those in the group with higher iron levels were able to perform this recognition memory task. A subset of this sample was tested at 12 months of age on a behavioral task designed to test declarative (explicit)

memory [28]. The IDM group was compared, in this case, to the non-IDM group rather than dividing them by ferritin levels. The IDM group had lower scores on the mental scale of the BSID-II and on the memory task relative to the controls (Fig. 2). It is important to note that these infants were not iron deficient at 9 months of age [29], and thus, the cognitive outcomes can be directly attributed to prenatal and neonatal iron status.

Iron is currently the quintessential nutrient for the discussion of timing, dose, and duration of deficiency. When a fetus is iron deficient for extended periods of time, brain development does not proceed on a typical trajectory and the suboptimal outcomes are most likely irreversible even when iron is replete. That said, iron accretion by the fetus in the third trimester is quite high, and once iron accumulates in the fetal brain, it does not deplete. Importantly, in the third trimester, the system pulls on maternal iron reserves that are acquired before conception. Women of child-bearing age need to consume appropriate amounts of bioavailable iron if they are to have the stores needed to support fetal development, especially if they plan to have another child before the stores have a chance to rebuild.

Docosahexaenoic Acid

The omega-3 fatty acid DHA (22:6n-3) is integral to cellular and neural function as it and other fatty acids comprise the phospholipid bilayer. The fetus requires high amounts of maternal fatty acids [30]. The demand is highest in the 3rd trimester, and multiple maternal pathways are upregulated to insure sufficient supply [31, 32]. Maternal DHA stores are mobilized in the 3rd trimester of pregnancy; maternal circulating levels of DHA decline progressively across pregnancy such that toward the end of pregnancy, maternal plasma levels of DHA are very low [33]. At birth, DHA levels in the infant are typically higher than in the mother [34], suggesting preferential transfer of DHA to the fetus. Materno-fetal transfer takes precedence over the maintenance of maternal DHA levels.

Whether there are any effects of maternal supplementation with fatty acids on infant cognition has been called into question by systematic reviews [35, 36]. Maternal DHA studies (supplementation or associative designs) have been completed with mixed results. Positive effects have been found on infant problem-solving [37], preschool-age processing [38], elementary-age verbal abilities [39] and full scale IQ [40], whereas no effects were found on global cognitive function [41–46], recognition memory [37], visual acuity [47], language [42, 43], attention [48], or working memory/inhibitory control [48]. Negative effects have been reported on mathematical abilities [39]. However, positive effects have been found in the reduction in risk of neurological disorders [49], language dis-

Fig. 2. Data from DeBoer et al. [28] on explicit memory performance for IDM at 12 months of age. Infants were tested on performance immediately after the researcher-modeled 2-step events and after a 10-min delay. Participants were scored on whether they performed the actions ($n = 2$) and whether they performed the actions in the proper order after a 10-min delay ($n = 1$). Performance was significantly different on the most difficult part of the task – getting the actions in the proper order after the delay (* $p < 0.05$). Immed, immediately; IDM, infants of diabetic mothers.

orders [50], autism spectrum disorder [51], and developmental delays [42]. Taken together, no definitive conclusions can be drawn from the maternal supplementation literature.

There are potential confounding variables that may help explain the lack of consistency in the results of fatty acid supplementation studies. First and foremost, positive effects of gestational supplementation have been found longitudinally when the offspring reach school age [38, 52]. It is possible that the effects of DHA on the fetal brain do not become apparent until the higher-order cognitive abilities known as executive functions (i.e., working memory, inhibitory control, planning, etc.) begin to come online. In addition, the seeming lack of discernable effects in the early months of life could be because the researchers utilize global assessments [41–46] rather than assessing specific cognitive effects, such as hippocampal function. Indeed, Levitsky and Strupp [53], in a meta-analysis, found that nutrition deficiencies do not result in whole-brain issues, but rather have very specific effects in the hippocampus, cerebellum, and neurotransmitter function. Thus, trials should be conducted based on hypotheses of specific effects on cognition.

Another confounder in the trials is the significant genetic component, which has historically been an unobserved variable in fatty acid studies. Mammals have the ability to metabolize DHA from the fatty acids found in plants (see Fig. 3 for pathways). The enzymes for the metabolic steps are coded by the *FADS* gene complex. Certain single nucleotide polymorphisms have been related to less than optimal action of this

metabolic pathway. Review of the genetics behind the conversion from α -linolenic acid (LNA; 18:3n-3) to DHA and the implications for subsequent brain function has been done [54] and, thus, it will not be covered here. In a related issue, the balance between the n-6 and n-3 pathways determines the metabolic progression as the pathways compete for enzymes. We have shown that cognitive abilities are compromised in the individual when the n-6:n-3 balance is off [55, 56]. Importantly, placental metabolism of fatty acids is differentially affected by imbalances between the n-6 and n-3 pathways [57, 58]. A correlational study was undertaken to explore the balance hypothesis in pregnant women and their subsequent children [59]. A higher n-6:n-3 ratio was found to be negatively correlated with language at 2 years of age and neurodevelopment in general at 3 years of age. Together, the evidence indicates that study design, background diet, and background genetics are integral in the consideration of the effects of fatty acids on cognition. With attention to these confounders, the effects of maternal supplementation with DHA on the cognitive abilities of the subsequent infants may become clear.

Choline

Choline is a micronutrient that is found in, for example, meat, legumes, and eggs. It is needed during pregnancy as it is the seminal source of its metabolites that are used in the development of all tissues, the synthesis of the neurotransmitter acetylcholine, the methylation of genes (epigenetics), and, in general, the one-carbon metabolic pathway. Phosphatidylcholine is a phospholipid that is used in the development of the brain and other tissues and as such is in high demand during gestation. There is a large body of animal work in support of maternal supplementation during fetal development, but the effects are not apparent until older age in the rodent models. Clinical trials in humans are few due to ethical concerns surrounding the choline status of women who would be randomly assigned to the control group. Supplementation with twice the recommended amount of choline (930 mg/day) during the third trimester resulted in improved speed of processing in infants [60], whereas supplementation with a lesser amount (750 mg/day) did not improve memory [61]. In the former study [60], background choline was carefully controlled. In the latter [61], background choline was already adequate. Estrogen up-regulates the metabolism of choline via the *PMT* gene, and thus, when background choline is adequate, the system is poised through up-regulation to provide for the needs of the fetus. Alternatively, and as would be predicted by the thrifty hypothesis, fetal programming may have set the fetus to expect extra choline in the environment, and in the absence of that, a mismatch occurred resulting in sub-optimal cognitive abilities.

Summary

As mentioned, all nutrients are no doubt important during pregnancy. It is important that women of child-bearing age understand that optimal nutrition during pregnancy will set their infants on a trajectory of health for the lifespan. Just as important is postnatal nutrition. Brain development does not stop until into the second decade of life (at which point optimal nutrition is then needed to protect against the onset of aging). Moreover, as mentioned, it is possible that a match between pre- and postnatal nutrition is important to development. We now move to a discussion of the evidence for postnatal nutrients that support brain development and function.

It is important that women of child-bearing age understand that optimal nutrition during pregnancy will set their infants on a trajectory of health for the lifespan

Importance of Postnatal Nutrition

Brain development continues into the second decade of life, and arguably, optimal nutrition is needed to support the brain not only during that period of time, but across the lifespan. That said, postnatally, the brain is most rapidly developing and most plastic during infancy and toddlerhood. Optimal nutrition in the fetal period and the first few years of life is central to the development of neural substrate on which a lifetime of cognition is based. There are sensitive periods in which certain nutrients may be more salient than at other times. For the most part, the same nutrients that have been studied in relation to prenatal development are integral to postnatal brain development. Thus, in this section, the utility of iron, choline, and DHA for postnatal brain development and function will be summarized.

Iron

As has been discussed, the timing, dose, and duration of deficiencies in relation to sensitive periods determines the extent and severity of the effects [1]. Iron deficiency during infancy appears to cause long-lasting and irreparable damage to neural tissue and neurotransmitter function. Iron deficiency at 9 months of age has been related to concurrent delays

in memory and attention development [62, 63]. Scientists following up a cohort in Chile have shown that infants who were identified as iron deficient with anemia (IDA) in infancy and were subsequently supplemented with iron for a minimum of 6 months [64] evidenced issues with inhibitory control and reaction time at 10 years of age [65] relative to a non-IDA comparison group. Similarly, in a sample from Costa Rica [66], those who had experienced IDA in infancy evidenced issues with executive functions and memory at 19 years of age relative to the controls [67]. In the latter study, interim follow-up sessions had documented that the IDA from infancy was no longer evident at 5, 11–14, and 19 years of age. With all appropriate covariates controlled, the source of the documented cognitive issues is most likely the IDA in infancy. As evidenced, timing of the deficiency is, therefore, important.

The background environment cannot be dismissed when considering iron deficiencies. Whereas it is true that those who are iron deficient more often than not are also living in less-than-optimal conditions, the statistical inclusion of replete comparison groups from similar environments in the described studies lends validity to the conclusions. Children adopted into the United States from other countries experience sudden and complete change in their environments. In a sample of international adoptees [68], it has been shown that regardless of country of origin (Ethiopia, China, post-Soviet) or length of institutionalization before adoption (52–91 months), those who were iron deficient on arrival in the United States performed less well on a battery of neurodevelopmental tests at baseline (arrival) and 6 months later relative to a comparison group matched for post-adoption socio-economic status. Importantly, the deficiencies were not completely remediated after 6 months even though they were in stable homes with proper nutrition. Two and a half to five years after adoption, another sample [69] evidenced a higher incidence of ADHD relative to controls that had not resolved in the post-adoption phase, whereas IQ scores had improved. Importantly, in this sample, longer periods of institutionalization and more severe iron deficiency predicted lower IQ [70].

Because preference is afforded the red blood cells when ferritin is low, the brain is already severely iron deficient before a diagnosis of anemia is warranted [71]. Therefore, prevention is key. Supplementation of at-risk mothers, delayed clamping of the umbilical cord, and supplementation from birth of at-risk infants are suggested strategies [72]. However, it should be noted that supplementation of replete individuals or of children who live in areas where malaria is an issue is not advised [72].

Docosahexaenoic Acid

As has been described, DHA is integral to synaptic transmission and neuronal fluidity, which underlie all cognition. DHA is found in wild fatty fish, free-range eggs, and grass-fed meat. Intake country to country varies based mostly on whether the country's culture is fish focused. Results of studies conducted early on were mixed [73]. There was evidence of effects of exogenous DHA on visual acuity in early infancy [74–76], but the effects leveled off after 4 months of age [75], and reviewers of the literature did not find sufficient evidence of an effect [e.g., 77, 78]. Moreover, scientists conducting randomized controlled trials (RCTs) of the effects of exogenous DHA on the cognitive development of infants born full term reported inconsistent results [for review, see 73, 78]; fewer than 40% of RCT results showed an effect of DHA supplementation on cognition.

A decade later, the story is still the same: there is little concrete evidence that DHA or DHA supplementation positively affects brain development and function [79–81]. Recent reports are mixed. For example, in an RCT designed to supplement women pre- and postnatally with fish oil or a placebo, an effect was reported in communicative abilities at 4 months of age [82]. Conversely, DHA status at 9 months of age has been reported to be inversely related to communicative abilities at 3 years of age in females [83]. As another example, in a fish-eating country (Norway), naturally occurring maternal DHA levels in the 28th week of gestation and infant DHA levels at 3 months of age were related to infant problem-solving abilities at 12 months of age [84]. These women were presumably eating DHA foods throughout gestation and lactation. However, supplementation in pregnancy and lactation with DHA in another fish-eating country (the Netherlands) did not result in any differences between supplemented and controls when the children were 18 months of age [45]. It is possible that the background consumption of fish weekly was sufficient, and further supplementation of DHA was a redundancy.

However, importantly, an effect was seen when the analyses were completed on continuous data (rather than grouped) relating cord blood DHA to cognitive abilities at 18 months of age [45]. This result illustrates that the lack of a clear consensus in the field is most likely due to unobserved variables. Whereas it is true that heterogeneity in designs and inappropriate cognitive assessments (global vs. specific) are a pervasive issue in this literature [73], maternal and infant DHA status differ with respect to placental control of fatty acid conversion and transfer. As mentioned previously, there is a genetic component to fatty acid status that has proven to be very complex. Until recently, scientists have discounted the fact that humans can synthesize endogenous DHA from its precursor, LNA (Fig. 3). Conventional thought was that this conversion rate

Fig. 3. Metabolic pathways of the omega-6 (left) and omega-3 (right) fatty acids. Figure used with permission [56].

was so low that it was of little consequence (mean LNA:DHA rate ~0.047%; [85]). Nonetheless, if control groups include participants who are endogenously producing their own DHA, they are confounding the results. In non-fish-eating countries such as the United States and Australia, the ability to metabolically improve one's own DHA status is optimal in over 90% of the population. In a study where genetic status was controlled [86], it was shown that background genetics were related to maternal levels of fatty acids. No effect was noted on offspring cognitive abilities, but the study was conducted in a fish-eating country. In a study designed to assess both maternal genetics and infant methylation (fetal programming), we did find that maternal genetic status for a single nucleotide polymorphism (*FADS2* rs174575) and infant methylation on the promoter region of that gene predicted toddler cognitive performance [87]. Thus, genetics and epigenetics are important considerations in the characterization of participants in fatty acid studies, especially in relation to brain development.

Choline

Choline supplementation is most often investigated during gestation as the animal models suggest sensitive periods for fetal neural development. Supplementation studies in infants and toddlers are rare even though they are not achieving the recommended intake [88]. Higher betaine (choline metabolite) levels are related to better visuomotor development in toddlers [88]. Infant choline supplementation is beneficial in

neural inhibition development (presumably by improving acetylcholine receptor activation) that has been noted as a risk factor for schizophrenia [89]. Supplementation with phosphatidylcholine did not help with suspected cerebral palsy [90], and 2 years' choline with uridine supplementation did not remediate the sequelae of neonatal brain bleeds [91]. Attempts to rectify the damage exacted by fetal alcohol exposure have met with challenges, but with proper timing, choline supplementation may be useful. Again, supplementation during pregnancy has been shown to prevent effects of fetal alcohol exposure [92, 93]. Postnatal supplementation appears to mitigate symptomology, but only in the younger participants (2.5- to 4-year-olds) [94] and not in those 5–10 years old [94, 95]. Thus, there may be distinct sensitive, even critical, periods for choline supplementation.

Importantly, DHA, choline, and uridine appear to work synergistically in the support of plasticity in the brain. Animal models have shown that the improved plasticity results in increases in synapses, dendrites, and neurotransmitter activity when all 3 are supplemented [96]. The incremental improvement of plasticity is not sufficient to overcome brain damage [90, 91] but may be of import in at-risk infants. In a study of the effects of human milk nutrients on the brain development and subsequent cognitive function of 6-month-olds, we showed that DHA and choline work together in support of recognition memory [97]. Infants whose milk contained higher levels of both choline and DHA exhibited better recognition

Table 2. Documented utility in humans for nutrient intake that will support fetal and infant brain development and subsequent function

Developmental period	Nutrient	References on positive effects	References on null finding
Preconception	Choline and metabolites Iodine	[4–7] [8]	
Prenatal	Vitamin D Iron Docosahexaenoic acid Choline	[16, 19, 20, 21] [26–29] [37–40, 42, 49–51] [60]	[17, 18] [37, 41–48] [61]
Postnatal	Iron Docosahexaenoic acid Choline	[62–69] [74–76, 82, 84, 97] [88, 94, 97]	[45, 83] [94, 95]

memory relative to those whose mothers were producing milk that had lower levels of the 2 nutrients. With DHA dependent on phosphatidylcholine for transport to the brain, it stands to reason that the 2 are needed together in support of the development of neural structures. The mixed results in the RCT of DHA supplementation could be the result, in part, of unobserved background diet.

Summary

Most certainly, all nutrients are important in the construction and maintenance of a human. That said, a few common concepts have emerged from the few that have been studied extensively and reviewed here.

Timing, dose, and duration of nutrient intake is important. Sensitive periods for nutritive action exist, and some may even reach the level of critical periods, the latter meaning that if a certain nutrient is not received at a particular time (critical period), the results will be profound and irreversible.

Background genetics and epigenetics determine the individual's level of need and ability to metabolize a given nutrient.

Not only should background genetics always be considered, but also, full consideration should be given to the prenatal nutritional environment. Prenatal and postnatal nutrition should match as the fetus is most likely (and ideally) programmed epigenetically for a world that will provide a similar nutritional experience.

Nutrients do not appear in nature in isolation. Thus, it is safe to assume that they do not work in isolation. Nutrients are working synergistically and, as such, should be studied together. Reductionism has its place in research. Once the basics of a particular nutrient's mechanistic actions have been established, synergisms should be explored.

When considering the mixed results that seem to be the hallmark of nutrition research (see Table 2 for summary), it will be important to keep these concepts in mind.

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References

- Cheatham CL, Sesma HW, Bauer PJ, Georgieff M. The development of declarative memory in infants born preterm. *Adv Child Dev Behav*. 2010;38:111–35.
- Mitchell LE. Epidemiology of neural tube defects. *Am J Med Genet C Semin Med Genet*. 2005 May;135C(1):88–94.
- Hibbard BM. The role of folic acid in pregnancy; with particular reference to anaemia, abruption and abortion. *J Obstet Gynaecol Br Commonw*. 1964 Aug;71(4):529–42.
- Smithells RW, Sheppard S, Schorah CJ, Seller MJ, Nevin NC, Harris R, et al. Possible prevention of neural-tube defects by periconceptional vitamin supplementation. *Lancet*. 1980 Feb;1(8164):339–40.
- Smithells RW, Sheppard S, Wild J, Schorah CJ. Prevention of neural tube defect recurrences in Yorkshire: final report. *Lancet*. 1989 Aug;2(8661):498–9.

- 6 Laurence KM, James N, Miller MH, Tennant GB, Campbell H. Double-blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural-tube defects. *Br Med J (Clin Res Ed)*. 1981 May;282(6275):1509–11.
- 7 Shaw GM, Carmichael SL, Yang W, Selvin S, Schaffer DM. Periconceptional dietary intake of choline and betaine and neural tube defects in offspring. *Am J Epidemiol*. 2004 Jul;160(2):102–9.
- 8 Greene LS, Stanbury JB. A retrospective view of iodine deficiency, brain development, and behavior from studies in Ecuador. In: Stanbury JB, editor. *The damaged brain of iodine deficiency: Cognitive, behavioral, neuromotor, and educative aspects*. New York: Cognizant Communication Corporation; 1994. pp. 173–85.
- 9 Pharoah PO, Connelly KJ. Iodine deficiency in Papua New Guinea. In: Stanbury JB, editor. *The damaged brain of iodine deficiency: Cognitive, behavioral, neuromotor, and educative aspects*. New York: Cognizant Communication Corporation; 1994. pp. 299–305.
- 10 Barker DJ. Developmental origins of adult health and disease. *J Epidemiol Community Health*. 2004 Feb;58(2):114–5.
- 11 Armitage JA, Khan IY, Taylor PD, Nathanielsz PW, Poston L. Developmental programming of the metabolic syndrome by maternal nutritional imbalance: how strong is the evidence from experimental models in mammals? *J Physiol*. 2004 Dec;561(Pt 2):355–77.
- 12 Roseboom TJ, van der Meulen JH, Ravelli AC, Osmond C, Barker DJ, Bleker OP. Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. *Mol Cell Endocrinol*. 2001 Dec;185(1-2):93–8.
- 13 McGrath J, Eyles D, Mowry B, Yolken R, Buka S. Low maternal vitamin D as a risk factor for schizophrenia: a pilot study using banked sera. *Schizophr Res*. 2003 Sep;63(1-2):73–8.
- 14 Zeghoud F, Vervel C, Guillozo H, Walrant-Debray O, Boutignon H, Garabédian M. Subclinical vitamin D deficiency in neonates: definition and response to vitamin D supplements. *Am J Clin Nutr*. 1997 Mar;65(3):771–8.
- 15 Eyles D, Brown J, Mackay-Sim A, McGrath J, Feron F. Vitamin D3 and brain development. *Neuroscience*. 2003;118(3):641–53.
- 16 Keim SA, Bodnar LM, Klebanoff MA. Maternal and cord blood 25(OH)-vitamin D concentrations in relation to child development and behaviour. *Paediatr Perinat Epidemiol*. 2014 Sep;28(5):434–44.
- 17 McCarthy EK, Murray DM, Malvisi L, Kenny LC, O'B Hourihane J, Irvine AD, et al. Antenatal Vitamin D Status Is Not Associated with Standard Neurodevelopmental Assessments at Age 5 Years in a Well-Characterized Prospective Maternal-Infant Cohort. *J Nutr*. 2018 Oct;148(10):1580–6.
- 18 Gale CR, Robinson SM, Harvey NC, Javaid MK, Jiang B, Martyn CN, et al.; Princess Anne Hospital Study Group. Maternal vitamin D status during pregnancy and child outcomes. *Eur J Clin Nutr*. 2008 Jan;62(1):68–77.
- 19 Whitehouse AJ, Holt BJ, Serralha M, Holt PG, Kusel MM, Hart PH. Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. *Pediatrics*. 2012 Mar;129(3):485–93.
- 20 Morales E, Guxens M, Llop S, Rodríguez-Bernal CL, Tardón A, Ri-año I, et al.; INMA Project. Circulating 25-hydroxyvitamin D3 in pregnancy and infant neuropsychological development. *Pediatrics*. 2012 Oct;130(4):e913–20.
- 21 Morales E, Julvez J, Torrent M, Ballester F, Rodríguez-Bernal CL, Andiaarena A, et al. Vitamin D in Pregnancy and Attention Deficit Hyperactivity Disorder-like Symptoms in Childhood. *Epidemiology*. 2015 Jul;26(4):458–65.
- 22 Laxmaiah A, Arlappa N, Balakrishna N, Mallikarjuna Rao K, Galreddy C, Kumar S, et al. Prevalence and determinants of micronutrient deficiencies among rural children of eight states in India. *Ann Nutr Metab*. 2013;62(3):231–41.
- 23 Gupta PM, Hamner HC, Suchdev PS, Flores-Ayala R, Mei Z. Iron status of toddlers, nonpregnant females, and pregnant females in the United States. *Am J Clin Nutr*. 2017 Dec;106 Suppl 6:1640S–6S.
- 24 deBenoist BD, McLean E, Egll I, Cogswell M. Worldwide prevalence of anaemia 1993–2005: WHO global database on anaemia. World Health Organization; 2008.
- 25 Lozoff B, Georgieff MK. Iron deficiency and brain development. *Semin Pediatr Neurol*. 2006 Sep;13(3):158–65.
- 26 Wieggersma AM, Dalman C, Lee BK, Karlsson H, Gardner RM. Association of Prenatal Maternal Anemia With Neurodevelopmental Disorders. *JAMA Psychiatry*. 2019 Sep;76(12):1–12.
- 27 Siddappa AM, Georgieff MK, Wewerka S, Worwa C, Nelson CA, Deregner RA. Iron deficiency alters auditory recognition memory in newborn infants of diabetic mothers. *Pediatr Res*. 2004 Jun;55(6):1034–41.
- 28 DeBoer T, Wewerka S, Bauer PJ, Georgieff MK, Nelson CA. Explicit memory performance in infants of diabetic mothers at 1 year of age. *Dev Med Child Neurol*. 2005 Aug;47(8):525–31.
- 29 Georgieff MK, Wewerka SW, Nelson CA, Deregner RA. Iron status at 9 months of infants with low iron stores at birth. *J Pediatr*. 2002 Sep;141(3):405–9.
- 30 Herrera E, Amusquivar E. Lipid metabolism in the fetus and the newborn. *Diabetes Metab Res Rev*. 2000 May-Jun;16(3):202–10.
- 31 Postle AD, Al MD, Burdge GC, Hornstra G. The composition of individual molecular species of plasma phosphatidylcholine in human pregnancy. *Early Hum Dev*. 1995 Aug;43(1):47–58.
- 32 Burdge G. Alpha-linolenic acid metabolism in men and women: nutritional and biological implications. *Curr Opin Clin Nutr Metab Care*. 2004 Mar;7(2):137–44.
- 33 Hornstra G, Al MD, van Houwelingen AC, Foreman-van Drongelen MM. Essential fatty acids in pregnancy and early human development. *Eur J Obstet Gynecol Reprod Biol*. 1995 Jul;61(1):57–62.
- 34 Al MD, Hornstra G, van der Schouw YT, Bulstra-Ramakers MT, Huisjes HJ. Biochemical EFA status of mothers and their neonates after normal pregnancy. *Early Hum Dev*. 1990 Dec;24(3):239–48.
- 35 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 Mar;97(3):531–44.

- 36 Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. *Cochrane Database Syst Rev*. 2018 Nov;11:CD003402.
- 37 Judge MP, Harel O, Lammi-Keefe CJ. Maternal consumption of a docosahexaenoic acid-containing functional food during pregnancy: benefit for infant performance on problem-solving but not on recognition memory tasks at age 9 mo. *Am J Clin Nutr*. 2007 Jun;85(6):1572–7.
- 38 Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA. Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics*. 2003 Jan;111(1):e39–44.
- 39 van der Wurff IS, Bakker EC, Hornstra G, Kirschner PA, Gielen M, Godschalk RW, et al. Association between prenatal and current exposure to selected LCPUFAs and school performance at age 7. *Prostaglandins Leukot Essent Fatty Acids*. 2016 May;108:22–9.
- 40 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 Dec;98(6):1575–82.
- 41 Campoy C, Escolano-Margarit MV, Ramos R, Parrilla-Roure M, Csábi G, Beyer J, et al. Effects of prenatal fish-oil and 5-methyltetrahydrofolate supplementation on cognitive development of children at 6.5 y of age. *Am J Clin Nutr*. 2011 Dec;94(6 Suppl):1880S–8S.
- 42 Makrides M, Gibson RA, McPhee AJ, Yelland L, Quinlivan J, Ryan P, et al.; DOMInO Investigative Team. Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children: a randomized controlled trial. *JAMA*. 2010 Oct;304(15):1675–83.
- 43 Meldrum S, Dunstan JA, Foster JK, Simmer K, Prescott SL. Maternal fish oil supplementation in pregnancy: a 12 year follow-up of a randomised controlled trial. *Nutrients*. 2015 Mar;7(3):2061–7.
- 44 Rioux FM, Bélanger-Plourde J, Leblanc CP, Vigneau F. Relationship between maternal DHA and iron status and infants' cognitive performance. *Can J Diet Pract Res*. 2011;72(2):76.
- 45 van Goor SA, Dijck-Brouwer DA, Erwich JJ, Schaafsma A, Hadjers-Algra M. The influence of supplemental docosahexaenoic and arachidonic acids during pregnancy and lactation on neurodevelopment at eighteen months. *Prostaglandins Leukot Essent Fatty Acids*. 2011 May–Jun;84(5–6):139–46.
- 46 Brouwer-Brolsma EM, van de Rest O, Godschalk R, Zeegers MP, Gielen M, de Groot RH. Associations between maternal long-chain polyunsaturated fatty acid concentrations and child cognition at 7 years of age: the MEFAB birth cohort. *Prostaglandins Leukot Essent Fatty Acids*. 2017 Nov;126:92–7.
- 47 Smithers LG, Gibson RA, Makrides M. Maternal supplementation with docosahexaenoic acid during pregnancy does not affect early visual development in the infant: a randomized controlled trial. *Am J Clin Nutr*. 2011 Jun;93(6):1293–9.
- 48 Gould JF, Makrides M, Colombo J, Smithers LG. Randomized controlled trial of maternal omega-3 long-chain PUFA supplementation during pregnancy and early childhood development of attention, working memory, and inhibitory control. *Am J Clin Nutr*. 2014 Apr;99(4):851–9.
- 49 Escolano-Margarit MV, Ramos R, Beyer J, Csábi G, Parrilla-Roure M, Cruz F, et al. Prenatal DHA status and neurological outcome in children at age 5.5 years are positively associated. *J Nutr*. 2011 Jun;141(6):1216–23.
- 50 Mulder KA, King DJ, Innis SM. Omega-3 fatty acid deficiency in infants before birth identified using a randomized trial of maternal DHA supplementation in pregnancy. *PLoS One*. 2014 Jan;9(1):e83764.
- 51 Lyall K, Munger KL, O'Reilly EJ, Santangelo SL, Ascherio A. Maternal dietary fat intake in association with autism spectrum disorders. *Am J Epidemiol*. 2013 Jul;178(2):209–20.
- 52 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 Apr;21(7):1504–12.
- 53 Levitsky DA, Strupp BJ. Malnutrition and the brain: changing concepts, changing concerns. *J Nutr*. 1995 Aug;125(8 Suppl):2212S–20S.
- 54 Conway MC, McSorley EM, Mulhern MS, Strain JJ, van Wijn-gaarden E, Yeates AJ. Influence of fatty acid desaturase (FADS) genotype on maternal and child polyunsaturated fatty acids (PUFA) status and child health outcomes: a systematic review. *Nutr Rev*. 2020 Jan;nuz086.
- 55 Sheppard KW, Cheatham CL. Executive functions and the w-6-to-w-3 fatty acid ratio: a cross-sectional study. *Am J Clin Nutr*. 2017 Jan;105(1):32–41.
- 56 Sheppard KW, Cheatham CL. Omega-6 to omega-3 fatty acid ratio and higher-order cognitive functions in 7- to 9-y-olds: a cross-sectional study. *Am J Clin Nutr*. 2013 Sep;98(3):659–67.
- 57 Haggarty P, Page K, Abramovich DR, Ashton J, Brown D. Long-chain polyunsaturated fatty acid transport across the perfused human placenta. *Placenta*. 1997 Nov;18(8):635–42.
- 58 Haggarty P, Ashton J, Joynson M, Abramovich DR, Page K. Effect of maternal polyunsaturated fatty acid concentration on transport by the human placenta. *Biol Neonate*. 1999;75(6):350–9.
- 59 Bernard JY, De Agostini M, Forhan A, de Lauzon-Guillain B, Charles MA, Heude B; EDEN Mother-Child Cohort Study Group. The dietary n6:n3 fatty acid ratio during pregnancy is inversely associated with child neurodevelopment in the EDEN mother-child cohort. *J Nutr*. 2013 Sep;143(9):1481–8.
- 60 Caudill MA, Strupp BJ, Muscalu L, Nevins JE, Canfield RL. Maternal choline supplementation during the third trimester of pregnancy improves infant information processing speed: a randomized, double-blind, controlled feeding study. *FASEB J*. 2018 Apr;32(4):2172–80.
- 61 Cheatham CL, Goldman BD, Fischer LM, da Costa KA, Reznick JS, Zeisel SH. Phosphatidylcholine supplementation in pregnant women consuming moderate-choline diets does not enhance infant cognitive function: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr*. 2012 Dec;96(6):1465–72.
- 62 Burden MJ, Westerlund AJ, Armony-Sivan R, Nelson CA, Jacobson SW, Lozoff B, et al. An event-related potential study of attention and recognition memory in infants with iron-deficiency anemia. *Pediatrics*. 2007 Aug;120(2):e336–45.

- 63 Carter RC, Jacobson JL, Burden MJ, Armony-Sivan R, Dodge NC, Angelilli ML, et al. Iron deficiency anemia and cognitive function in infancy. *Pediatrics*. 2010 Aug;126(2):e427–34.
- 64 Algarín C, Peirano P, Garrido M, Pizarro F, Lozoff B. Iron deficiency anemia in infancy: long-lasting effects on auditory and visual system functioning. *Pediatr Res*. 2003 Feb;53(2):217–23.
- 65 Algarín C, Nelson CA, Peirano P, Westerlund A, Reyes S, Lozoff B. Iron-deficiency anemia in infancy and poorer cognitive inhibitory control at age 10 years. *Dev Med Child Neurol*. 2013 May;55(5):453–8.
- 66 Lozoff B, Brittenham GM, Wolf AW, McClish DK, Kuhnert PM, Jimenez E, et al. Iron deficiency anemia and iron therapy effects on infant development test performance. *Pediatrics*. 1987 Jun;79(6):981–95.
- 67 Lukowski AF, Koss M, Burden MJ, Jonides J, Nelson CA, Kaciroti N, et al. Iron deficiency in infancy and neurocognitive functioning at 19 years: evidence of long-term deficits in executive function and recognition memory. *Nutr Neurosci*. 2010 Apr;13(2):54–70.
- 68 Fuglestad AJ, Kroupina MG, Johnson DE, Georgieff MK. Micronutrient status and neurodevelopment in internationally adopted children. *Acta Paediatr*. 2016 Feb;105(2):e67–76.
- 69 Doom JR, Georgieff MK, Gunnar MR. Institutional care and iron deficiency increase ADHD symptomology and lower IQ 2.5–5 years post-adoption. *Dev Sci*. 2015 May;18(3):484–94.
- 70 Doom JR, Gunnar MR, Georgieff MK, Kroupina MG, Frenn K, Fuglestad AJ, et al. Beyond stimulus deprivation: iron deficiency and cognitive deficits in postinstitutionalized children. *Child Dev*. 2014 Sep-Oct;85(5):1805–12.
- 71 Georgieff MK. Iron assessment to protect the developing brain. *Am J Clin Nutr*. 2017 Dec;106 Suppl 6:1588S–93S.
- 72 Cusick SE, Georgieff MK, Rao R. Approaches for Reducing the Risk of Early-Life Iron Deficiency-Induced Brain Dysfunction in Children. *Nutrients*. 2018 Feb;10(2):E227.
- 73 Cheatham CL. Omega-3 fatty acids and the development of cognitive abilities: a review of DHA supplementation studies. *Perspect Agric Vet Sci Nutr Nat Resour*. 2008;3(1):1–15.
- 74 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 Oct;143(4 Suppl):S17–25.
- 75 SanGiovanni JP, Berkey CS, Dwyer JT, Colditz GA. Dietary essential fatty acids, long-chain polyunsaturated fatty acids, and visual resolution acuity in healthy fullterm infants: a systematic review. *Early Hum Dev*. 2000 Mar;57(3):165–88.
- 76 SanGiovanni JP, Parra-Cabrera S, Colditz GA, Berkey CS, Dwyer JT. Meta-analysis of dietary essential fatty acids and long-chain polyunsaturated fatty acids as they relate to visual resolution acuity in healthy preterm infants. *Pediatrics*. 2000 Jun;105(6):1292–8.
- 77 Schulzke SM, Patole SK, Simmer K. Long-chain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane Database Syst Rev*. 2011 Feb;(2):CD000375.
- 78 Simmer K, Patole SK, Rao SC. Long-chain polyunsaturated fatty acid supplementation in infants born at term [update of Cochrane Database Syst Rev. 2001;(4):CD000376; PMID: 11687076]. *Cochrane Database Syst Rev*. 2008 Jan;(1):CD000376.
- 79 Jasani B, Simmer K, Patole SK, Rao SC. Long chain polyunsaturated fatty acid supplementation in infants born at term. *Cochrane Database Syst Rev*. 2017 Mar;3:CD000376.
- 80 Moon K, Rao SC, Schulzke SM, Patole SK, Simmer K. Longchain polyunsaturated fatty acid supplementation in preterm infants. *Cochrane Database Syst Rev*. 2016 Dec;12:CD000375.
- 81 Meldrum S, Simmer K. Docosahexaenoic Acid and Neurodevelopmental Outcomes of Term Infants. *Ann Nutr Metab*. 2016;69 Suppl 1:22–8.
- 82 Ostadrahimi A, Salehi-Pourmehr H, Mohammad-Alizadeh-Charandabi S, Heidarabady S, Farshbaf-Khalili A. The effect of perinatal fish oil supplementation on neurodevelopment and growth of infants: a randomized controlled trial. *Eur J Nutr*. 2018 Oct;57(7):2387–97.
- 83 Engel S, Tronhjelm KM, Hellgren LI, Michaelsen KF, Lauritzen L. Docosahexaenoic acid status at 9 months is inversely associated with communicative skills in 3-year-old girls. *Matern Child Nutr*. 2013 Oct;9(4):499–510.
- 84 Braarud HC, Markhus MW, Skotheim S, Stormark KM, Frøyland L, Graff IE, et al. Maternal DHA Status during Pregnancy Has a Positive Impact on Infant Problem Solving: A Norwegian Prospective Observation Study. *Nutrients*. 2018 Apr;10(5):E529.
- 85 Pawlosky RJ, Hibbeln JR, Novotny JA, Salem N Jr. Physiological compartmental analysis of alpha-linolenic acid metabolism in adult humans. *J Lipid Res*. 2001 Aug;42(8):1257–65.
- 86 Yeates AJ, Love TM, Engström K, Mulhern MS, McSorley EM, Grzesik K, et al. Genetic variation in FADS genes is associated with maternal long-chain PUFA status but not with cognitive development of infants in a high fish-eating observational study. *Prostaglandins Leukot Essent Fatty Acids*. 2015 Dec;102–103:13–20.
- 87 Cheatham CL, Lupu DS, Niculescu MD. Genetic and epigenetic transgenerational implications related to omega-3 fatty acids. Part II: maternal FADS2 rs174575 genotype and DNA methylation predict toddler cognitive performance. *Nutr Res*. 2015 Nov;35(11):948–55.
- 88 Wiedeman AM, Chau CM, Grunau RE, McCarthy D, Yurko-Mauro K, Dyer RA, et al. Plasma Betaine Is Positively Associated with Developmental Outcomes in Healthy Toddlers at Age 2 Years Who Are Not Meeting the Recommended Adequate Intake for Dietary Choline. *J Nutr*. 2018 Aug;148(8):1309–14.
- 89 Ross RG, Hunter SK, McCarthy L, Beuler J, Hutchison AK, Wagner BD, et al. Perinatal choline effects on neonatal pathophysiology related to later schizophrenia risk. *Am J Psychiatry*. 2013 Mar;170(3):290–8.
- 90 Andrew MJ, Parr JR, Montague-Johnson C, Laler K, Qi C, Baker B, et al. Nutritional intervention and neurodevelopmental outcome in infants with suspected cerebral palsy: the Dolphin infant double-blind randomized controlled trial. *Dev Med Child Neurol*. 2018 Sep;60(9):906–13.
- 91 Andrew MJ, Parr JR, Montague-Johnson C, Laler K, Holmes J, Baker B, et al. Neurodevelopmental outcome of nutritional intervention in newborn infants at risk of neurodevelopmental impairment: the Dolphin neonatal double-blind randomized controlled trial. *Dev Med Child Neurol*. 2018 Sep;60(9):897–905.

- 92 Jacobson SW, Carter RC, Molteno CD, Stanton ME, Herbert JS, Lindinger NM, et al. Efficacy of maternal choline supplementation during pregnancy in mitigating adverse effects of prenatal alcohol exposure on growth and cognitive function: A randomized, double-blind, placebo-controlled clinical trial. [Alcohol Clin Exp Res](#). 2018 Jul;42(7):1327–41.
- 93 Coles CD, Kable JA, Keen CL, Jones KL, Wertelecki W, Granovska IV, et al.; CIFASD. Dose and Timing of Prenatal Alcohol Exposure and Maternal Nutritional Supplements: Developmental Effects on 6-Month-Old Infants. [Matern Child Health J](#). 2015 Dec;19(12):2605–14.
- 94 Wozniak JR, Fuglestad AJ, Eckerle JK, Fink BA, Hoecker HL, Boys CJ, et al. Choline supplementation in children with fetal alcohol spectrum disorders: a randomized, double-blind, placebo-controlled trial. [Am J Clin Nutr](#). 2015 Nov;102(5):1113–25.
- 95 Nguyen TT, Risbud RD, Mattson SN, Chambers CD, Thomas JD. Randomized, double-blind, placebo-controlled clinical trial of choline supplementation in school-aged children with fetal alcohol spectrum disorders. [Am J Clin Nutr](#). 2016 Dec;104(6):1683–92.
- 96 Wurtman RJ, Cansev M, Sakamoto T, Ulus IH. Administration of docosahexaenoic acid, uridine and choline increases levels of synaptic membranes and dendritic spines in rodent brain. [World Rev Nutr Diet](#). 2009;99:71–96.
- 97 Cheatham CL, Sheppard KW. Synergistic effects of human milk nutrients in the support of infant recognition memory: an observational study. [Nutrients](#). 2015 Nov;7(11):9079–95.