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.

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...
Early Brain Development

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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

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### Table 1. Examples of natural sources of select nutrients

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

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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
Maternal vitamin D status and cord blood vitamin D levels are related to better pregnancy.

It would not be ethical to randomize women to remain deficient throughout research in humans has been correlational; it would not be ethical to randomize women to remain deficient throughout pregnancy. 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 vitamin 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 iron 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. Maternal-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 disorders [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 PEMT 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 suboptimal 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 experienced 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...
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
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.

**Disclosure Statement**

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

<table>
<thead>
<tr>
<th>Developmental period</th>
<th>Nutrient</th>
<th>References on positive effects</th>
<th>References on null finding</th>
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<tbody>
<tr>
<td>Preconception</td>
<td>Choline and metabolites</td>
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<td></td>
<td>Iodine</td>
<td></td>
<td>[8]</td>
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<td>Vitamin D</td>
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<td></td>
<td>Iron</td>
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<td>[37, 40–42, 49–51]</td>
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<tr>
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<td>Docosahexaenoic acid</td>
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<td>[60]</td>
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**References**


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.


