

Nutrition and brain development in early life

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Presented here is an overview of the pathway from early nutrient deficiency to long-term brain function, cognition, and productivity, focusing on research from low- and middle-income countries. Animal models have demonstrated the importance of adequate nutrition for the neurodevelopmental processes that occur rapidly during pregnancy and infancy, such as neuron proliferation and myelination. However, several factors influence whether nutrient deficiencies during this period cause permanent cognitive deficits in human populations, including the child's interaction with the environment, the timing and degree of nutrient deficiency, and the possibility of recovery. These factors should be taken into account in the design and interpretation of future research. Certain types of nutritional deficiency clearly impair brain development, including severe acute malnutrition, chronic undernutrition, iron deficiency, and iodine deficiency. While strategies such as salt iodization and micronutrient powders have been shown to improve these conditions, direct evidence of their impact on brain development is scarce. Other strategies also require further research, including supplementation with iron and other micronutrients, essential fatty acids, and fortified food supplements during pregnancy and infancy.

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INTRODUCTION

Adequate nutrition is necessary for normal brain development. Nutrition is especially important during pregnancy and infancy, which are crucial periods for the formation of the brain, laying the foundation for the development of cognitive, motor, and socio-emotional skills throughout childhood and adulthood. Thus, nutritional deficiencies during pregnancy and infancy are likely to affect cognition, behavior, and productivity throughout the school years and adulthood. Focusing on this early period for the prevention of nutrient deficiencies may have long-term and widespread benefits for individuals and societies.

This article presents an overview of the pathway from early nutritional deprivation to long-term brain function, cognition, behavior, and productivity. Although nutrition is important for brain function throughout the

lifespan, this article focuses on nutrition during pregnancy and the first few years after birth, which is the period of most rapid brain development. Presented first are the biological mechanisms through which nutrient deficiencies in pregnancy and infancy may affect brain development. Most of this evidence at the cellular and molecular level is from animal studies. Although these animal models have demonstrated the importance of adequate nutrition for the developing brain, many factors influence whether undernutrition during pregnancy and infancy leads to permanent cognitive deficits in human populations. The second part of this article discusses four of those factors: 1) the amount and quality of stimulation the child receives from the environment; 2) the timing of nutrient deprivation; 3) the degree of nutrient deficiency; and 4) the possibility of recovery. Finally, a brief review of human studies is presented, focusing on research from low- and middle-income countries, where multiple

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267

nutrient deficiencies are prevalent among pregnant women and children.¹ Also addressed in this review are the long-term consequences of undernutrition in early life, randomized trials of food and protein/energy supplementation, and studies of breastfeeding practices, essential fatty acids, and certain specific micronutrients, in addition to implications for policy, programs, and future research.

ROLE OF NUTRIENTS IN BRAIN DEVELOPMENT

Approximately 22 days after conception, the neural plate begins to fold inward, forming the neural tube, which eventually becomes the brain and spinal cord.² Adequate nutrition is necessary from the beginning, with the formation of the neural plate and neural tube affected by nutrients such as folic acid, copper, and vitamin A. Seven weeks after conception, cell division begins within the neural tube, creating nerve cells (neurons) and glial cells (cells that support neurons). After a neuron is created, it migrates to its place in the brain, where it then grows axons and dendrites projecting out from its cell body. These branching projections make connections with other cells, called synapses, through which nerve signals travel from one cell to another. These neurodevelopmental processes begin during gestation and continue throughout infancy (see Table 1). Groups of neurons form pathways, which are refined through the programmed elimination of cells and connections. About half of all the cells that are produced in the brain are subsequently eliminated throughout childhood and adolescence. Synapses are also overproduced and then selectively eliminated. Some of this refining of neural pathways depends on the child's experience, or in other words, input from the child's environment. Cells and connections that are activated are retained and strengthened while those that are not used are eliminated. This is thought to be one of the primary mechanisms of brain plasticity, allowing the brain to organize itself to adapt to the environment and reorganize itself to recover from injury during development.²

Evidence from animal models of nutrient deficiency, and some evidence from human studies, clearly shows that many nutrients are necessary for brain development. Table 1 presents evidence for the effect of specific nutrient deficiencies during early development on five key neurodevelopmental processes: 1) neuron proliferation, 2) axon and dendrite growth, 3) synapse formation, pruning, and function, 4) myelination, and 5) neuron apoptosis (programmed cell death). Table 1 focuses on nutrients that have been studied in human as well as animal studies. Other nutrients, such as copper, which is also important for some of these neurodevelopmental

processes, are not included since rigorous studies in human populations and intervention studies have not yet been conducted.

Although the necessity of nutrients for brain development is evident, the extent to which nutrient deprivation during gestation and infancy results in long-term effects on brain function in free-living human populations is not yet clear. The actual impact depends on several factors, including 1) the child's experience and input from the environment, 2) the timing of nutrient deprivation, 3) the degree of nutrient deficiency, and 4) the possibility of recovery. Each of these factors is discussed in the following sections, followed by a brief discussion of methodological factors that can also influence the results of nutrition studies.

FACTORS INFLUENCING THE IMPACT OF UNDERNUTRITION

Experience and input from the environment

Brain development is affected by experience. Two types of processes are described as "experience-expectant" and "experience-dependent."⁴¹ In experience-expectant processes, the brain relies on specific input for normal development. For example, the brain expects visual input through the optic nerve for normal development of the visual cortex.⁴¹ The absence of these expected experiences impairs the neurodevelopmental processes that depend on them. These experience-expectant processes also depend on other types of sensory stimulation (e.g., auditory and tactile) and occur early in life. In contrast, "experience-dependent" processes refer to the way the brain organizes itself in response to an individual's experiences and acquired skills, which is a process that continues throughout the lifespan. For example, a neuroimaging study demonstrated that the rear hippocampus, a part of the brain that underlies spatial memory, increased in volume as London taxi-driver trainees learned the layout of the city streets.⁴⁷ While experience-expectant mechanisms refer to features of the environment that are (or should be) universal, experience-dependent mechanisms refer to aspects of the environment that are unique to the individual. These latter processes enable individuals to adapt to and thrive in their specific culture and environment.

Adequate nutrition can be considered an aspect of the environment that is expected by the brain for normal development.⁴⁸ An environment with poor quality and variety of sensory and social input impairs some of the same neurodevelopmental processes as nutrient deprivation during early development, including the complexity of dendritic branching and synaptic density (Table 1).

Table 1 Evidence for the role of selected nutrients and experience in five key neurodevelopmental processes.

Influence	Neurodevelopmental processes			
	Axon and dendrite growth	Synapse formation, pruning, and function	Myelination	Apoptosis
Definition and timing	<p>Neuron proliferation</p> <p>Neuron proliferation is the creation of new cells through cell division. This begins in week 7 of gestation and continues to at least 4.5 months postpartum.² Neuron proliferation is mostly completed at birth, but neurons can be created in adulthood.³</p>	<p>Synapses are connections between axons, dendrites, and cell bodies. Synapse formation begins during gestation (around week 23) and continues throughout the lifespan. Synaptic density reaches a peak at different times in different brain areas (for example, in the visual cortex between 4 and 12 months postpartum, and in the prefrontal cortex after 15 months postpartum).² The decrease in synaptic density that follows this peak in each area reflects synaptic pruning. Synapse overproduction is completed in the second year after birth, while synaptic pruning begins in the first year after birth and continues through adolescence.²</p>	<p>Myelin is white, fatty matter that covers axons and accelerates the speed of nerve impulses traveling from one cell to another. Myelination begins as early as 12–14 weeks of gestation in the spinal cord and continues until adulthood. The most significant period of myelination occurs from mid-gestation to age 2 years.⁴ Before birth, myelination occurs in brain areas involved in orientation and balance. After birth, the rate of myelination of areas involved in vision and hearing reaches a peak before myelination of areas underlying language, coinciding with the emergence of these abilities.²</p>	<p>Apoptosis is programmed cell death. Of all the cells that are produced in the brain, about half die through a variety of mechanisms. One of these mechanisms is programmed cell death, which is regulated primarily by neurotrophic factors, such as BDNF and IGF-1. When levels of neurotrophic factors are below a certain threshold, molecules within the cell trigger degeneration. Neuron apoptosis coincides with the period of synaptogenesis, beginning during gestation and continuing through adolescence.⁵ Small head size or brain volume may be caused by decreased neuron proliferation or increased apoptosis.</p>
Protein-energy malnutrition	<p>A human autopsy study showed that 3–4-month-old infants with moderate malnutrition (low weight for age) had decreased dendritic span and arborization (complexity of branching projections) compared to well-nourished infants.⁹ Rodent models have found similar effects of early postnatal undernutrition on dendrite growth.¹⁰</p>	<p>Both prenatal and postnatal undernutrition in rodents results in fewer synapses as well as synaptic structural changes.^{a1,12}</p>	<p>Adults who had been exposed to famine in utero in Holland during World War II showed increased white matter hyperintensities, shown by MRI.¹³ Reduced myelination has been found in animal models of IUGR⁶ and maternal nutrient restriction without resulting in IUGR.¹⁴ IUGR decreases IGF-1 levels and IGF-1-binding protein expression,⁶ which influence myelin production.⁹</p>	<p>BDNF and IGF-1 levels decreased and cell death increased in the offspring of baboon mothers fed a nutrient-restricted diet during pregnancy (without IUGR).¹⁴ Other animal models have also shown that IUGR decreases IGF-1 and IGF-1-binding protein expression.⁶</p>
Fatty acids	<p>Neurogenesis requires the synthesis of large amounts of membrane phospholipid from fatty acids. Reduced neuron proliferation has been shown in animals with gestational DHA deficiency.¹⁵</p>	<p>Arachidonic acid and docosahexaenoic acid (DHA) in membranes at synaptic sites play a role in the maturation of synapses and in neurotransmission.¹⁶</p>	<p>Fatty acids are structural components of myelin. Both prenatal and postnatal fatty acid deficiency in rodents reduces the amount and alters the composition of myelin.^{17,18}</p>	
Iron	<p>Iron is required for the enzyme ribonucleotide reductase that regulates central nervous system cell division.⁶ While gestational and neonatal iron deficiency in rodents does not affect overall brain size, a decrease in the size of the hippocampus (a subcortical structure that underlies learning and memory) has been shown.¹⁹</p>	<p>Gestational and early postnatal iron deficiency in rodents results in decreased synaptic maturity and efficacy in the hippocampus, which persists despite iron repletion.²¹ In adult rodents, iron deficiency decreases the number of dopamine D2 receptors and the density of dopamine transporter in the striatum and nucleus accumbens.²² In both animal models and cell culture experiments, dopamine and norepinephrine metabolism are altered by iron deficiency.²³</p>	<p>Iron plays a role in myelin synthesis. In animal models, even marginal iron deficiency during prenatal and early postnatal development decreases myelin synthesis and alters myelin composition, which is not corrected with iron repletion.²⁴</p>	

Table 1 Continued

Neurodevelopmental processes		Apoptosis	
Influence	Neuron proliferation	Synapse formation, pruning, and function	Myelination
Iodine and thyroid hormones	Some fetuses aborted in months 6 and 8 of gestation in an iodine-deficient area of China had lower brain weight than fetuses in an iodine-sufficient area, while some showed increased cell density. Gestational iodine deficiency in sheep and marmosets resulted in reduced brain weight and cell number, which was not corrected with iodine repletion. No effect on brain weight or cell number was found in rodents with gestational iodine deficiency, but cell migration was impaired. ²⁵	Gestational iodine deficiency in sheep resulted in decreased synaptic density, which was not corrected with iodine repletion. ²⁵ Gestational and early postnatal hypothyroidism in rodents decreases the number and density of synapses in the cerebellum, and alters neurotransmitter levels. ²⁷	No myelination was detected in the cerebral cortex of fetuses aborted at month 8 of gestation in an iodine-deficient area of China. ²⁸ Gestational iodine deficiency in sheep and rodents reduces myelination. ²⁵ Gestational and early postnatal hypothyroidism in rodents leads to reduced myelination. ²⁷
Zinc	Zinc is necessary for cell division due to its role in DNA synthesis. Gestational zinc deficiency in rodents results in decreased number of cells, as reflected by total brain DNA ²⁹ and reduced regional brain mass in the cerebellum, limbic system, and cerebral cortex. ⁶	Zinc released into synapses in the hippocampus and cerebral cortex modulates synapse function. Specifically, zinc modulates postsynaptic NMDA receptors for glutamate and inhibits GABA _B receptor activation. ³⁰	In rodent pups, zinc deficiency decreased expression of IGF-1 and growth hormone receptor genes. ³¹
Choline	Choline is essential for stem cell proliferation and is involved in transmembrane signaling during neurogenesis. ⁶ In rodents, gestational choline supplementation stimulates cell division. ³²	The neurotransmitter acetylcholine is synthesized from choline. Gestational choline deficiency in rodents has long-term effects on cholinergic neurotransmission despite repletion. ³²	Gestational choline deficiency increases the rate of apoptosis in the hippocampus in rodents. ³²
B-vitamins	Before neuron proliferation begins, during weeks 2–4 of gestation, the neural tube forms, which is comprised of progenitor (stem) cells that give rise to neurons and glial cells (cells that support neurons). ² Maternal deficiency in folic acid and vitamin B ₁₂ is associated with neural tube defects, such as anencephaly and spina bifida. ³³	Gestational and early postnatal Vitamin B ₆ deficiency in rodents results in decreased synaptic density in the neocortex, ³⁵ reduced synaptic efficiency, particularly in NMDA receptors, ³⁶ and lowered dopamine levels and dopamine D2 receptor binding in the striatum. ³⁷	Gestational and early postnatal Vitamin B ₆ deficiency in rodents results in reduced myelination. ³⁸
Experience	Rodents raised in enriched environments (large enclosures with objects that allow visual and tactile stimulation) show greater brain weight and cortical thickness than rodents raised in impoverished environments (standard lab cages). ³⁹	Rodents raised in enriched environments (large enclosures with objects that allow visual and tactile stimulation) show more synapses per neuron in visual and motor cortices than rodents raised in impoverished environments (standard lab cages). ³⁹	Children raised in Romanian orphanages and then adopted into US families, thus having experienced a degree of early socioemotional deprivation, showed structural changes in white matter tracts compared to control children who had not spent any time in an orphanage. ⁴² Practicing the piano in childhood correlated with myelination in areas underlying finger movements, as measured by fractional anisotropy. ⁴³ An enriched rearing environment affects myelination of the corpus callosum in rodents and monkeys. ^{44,45}

⁴⁶The gestational period in rodents corresponds to the first half of pregnancy in humans, while the first 3 weeks after birth in rodents corresponds to the second half of pregnancy in humans.⁴⁶

Abbreviations: BDNF, brain-derived neurotrophic factor; GABA_B, gamma-aminobutyric acid B; IGF-1, insulin-like growth factor-1; IUGR, intrauterine growth restriction; NMDA, N-methyl-D-aspartate.

The parallel influences of nutrient deficiency and stimulation from the environment on brain development may operate in several ways: additive effects, interacting effects, and mediating effects, all of which have been demonstrated in empirical studies. These are depicted in Figure 1 and discussed in greater detail below.

Additive effects. Nutrient deficiency and experiential input from the environment may have independent additive effects on brain development. In this case, in an at-risk population, one would expect children with both risk factors (nutrient deficiency and low stimulation) to perform at low levels, children with one risk factor (nutrient deficiency or low stimulation) to perform at average levels, and children with neither risk factor (sufficient nutrition and high stimulation) to perform at high levels in cognitive, motor, and socioemotional development. This pattern is shown in Figure 1a. In support of this hypothesis, several studies have shown that nutritional supplementation and psychosocial stimulation together result in greater improvements in child development than either intervention alone.^{49,50} In these studies, psychosocial stimulation consisted of periodic home visits during which community workers facilitated play sessions with mothers and children. The community workers conducted activities such as demonstrating play with homemade toys, emphasizing the quality of the verbal interactions between mothers and children, and teaching concepts such as color, shape, size, and number. Children in Costa Rica showed similar additive effects of iron-deficiency anemia in infancy and low socioeconomic status on cognitive scores at school age.⁵¹

Interacting effects. Alternatively, nutrient deficiency or intervention may affect some children but not others, depending on the amount and quality of stimulation they receive. For example, in Chile, low-birth-weight infants born into families with high socioeconomic status were at lower risk for poor developmental outcomes than those born into disadvantaged environments.⁵² Similarly, in 6–8-year-old children in Vietnam, nutritional status was related to cognitive scores among children who did not participate in a preschool program at age 3–4 years, but not among those who did.⁵³ Thus, in some cases, stimulation from the environment can protect children from negative effects of undernutrition on development. This possibility is shown in Figure 1b. Conversely, undernourished children from disadvantaged homes where protective factors are lacking may show more of a developmental response to nutrition and other forms of interventions. For example, in Guatemala, the effect of a supplementary protein/energy drink on infant and preschool development was greatest among families of low

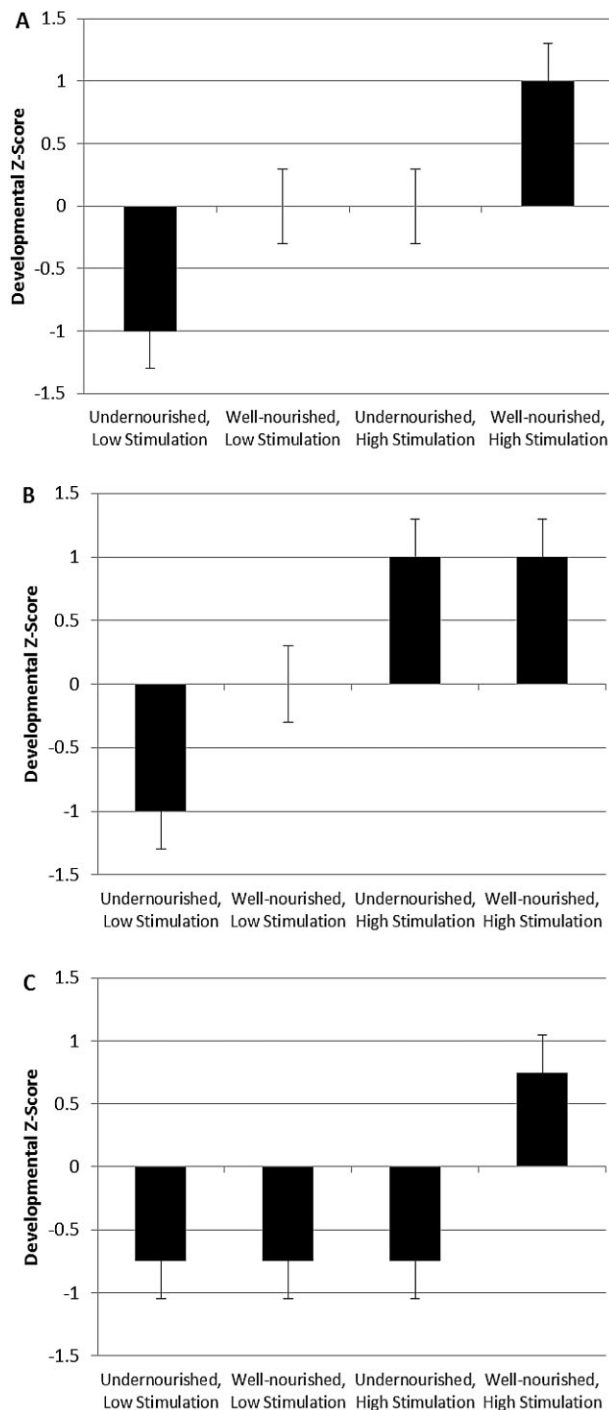


Figure 1 Three hypothetical scenarios in which the effects of undernutrition and a poor-quality environment may show additive or interacting effects on children's motor, cognitive, and socioemotional development. A Additive effects of undernutrition and poor-quality environment. **B** An enriched environment protects children from negative effects of undernutrition. **C** Nutrition intervention only affects children who have adequate stimulation, or stimulation intervention only affects children who have adequate nutrition.

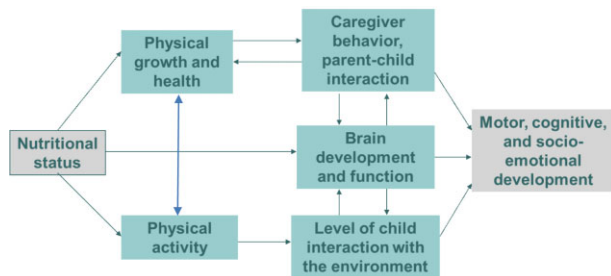


Figure 2 Hypothetical scenario in which the child's experience acts as a mediator between nutritional status and motor, cognitive, and socioemotional development. Adapted from Levitsky and Barnes⁵⁸ and Pollitt.⁵⁴

socioeconomic status.⁵⁴ In Chile, 1 year of weekly home visits providing psychosocial stimulation increased cognitive and socioemotional scores in infants with iron-deficiency anemia (IDA), but not in infants without IDA.⁵⁵

Another way that nutrition and stimulation may interact is that nutritional supplementation may only positively affect development among children who receive a certain amount of stimulation from the environment. If children do not receive any stimulation, improving nutrition alone may be insufficient to improve brain development. For example, in Jamaica, infants between the ages of 9 and 30 months who participated in a psychosocial stimulation intervention benefited from zinc supplementation, while those who did not receive psychosocial stimulation did not show any developmental benefit from supplementary zinc.⁵⁶ It is also possible that an intervention providing psychosocial stimulation may only benefit children who are adequately nourished. In an animal model of maternal choline deficiency, 7-month-old rodents were exposed to an environmental enrichment experience by being allowed to explore a maze once daily for 12 days. Rodents whose mothers had been given choline during gestation showed increased neurogenesis in the hippocampus through the enriching experience, while rodents whose mothers had been deprived of choline during gestation did not show altered neurogenesis.⁵⁷ This type of pattern is illustrated in Figure 1c.

Mediating effects. Finally, improving nutritional status may actually improve children's experiences and the stimulation they receive from the environment. Undernutrition affects physical growth, physical activity, and motor development, which may, in turn, influence brain development through two pathways. The first pathway is through caregiver behavior and the second is through child exploration of the environment^{54,58} (see Figure 2).

First, caregivers may treat children who are small for their age as younger than they actually are, and thus not provide age-appropriate stimulation, which could result in altered brain development. Also, undernourished children may be frequently ill and therefore fussy, irritable, and withdrawn, leading caregivers to treat them more negatively than they would treat a happy, healthy child. Reduced activity due to undernutrition may limit the child's exploration of the environment and initiation of caregiver interactions, which could also lead to poor brain development.⁵⁹ Some evidence suggests that these mechanisms contribute to delayed motor and cognitive development in infants and children with IDA.^{60,61} However, in stunted Jamaican infants, nutritional supplementation affected cognitive development but not activity levels, and activity and development were not related to each other, suggesting that this mechanism did not mediate the effect of nutrition on cognitive development in this cohort.⁶²

Few studies have examined the potential additive, interacting, and mediating effects of nutrition and experiential input from the environment on child motor, cognitive, and socioemotional development. Studies that have tested all of these in a systematic way could not be located in the existing literature. In future research, datasets that allow the testing of each of these hypotheses are needed.

Timing of nutrient deprivation or supplementation

Nutrient deficiency is more likely to impair brain development if the deficiency occurs during a time period when the need for that nutrient for neurodevelopment is high. Various nutrients are necessary for specific neurodevelopmental processes. Each process occurs in different, overlapping time periods in different brain areas. The timing of five key neurodevelopmental processes is presented in the first row of Table 1. Drawing links between specific nutrients, specific neurodevelopmental processes, and the time period of deprivation or supplementation allows specific hypotheses to be made concerning the effect of nutrient deprivation or supplementation on brain development.

For example, myelination of the brainstem auditory pathway occurs from week 26 of gestation until at least 1 year after birth.⁶³ Fatty acids such as docosahexaenoic acid (DHA) are necessary for myelination. This leads to the hypothesis that supplementation with DHA in the third trimester and the first year after birth may improve myelination of this auditory pathway. The latency of auditory-evoked potentials, which measure electrical activity in response to an auditory stimulus through electrodes placed on the scalp, is thought to reflect myelination, among other physiological aspects of

brain function.⁶⁴ In support of the effect of DHA on myelination of the brainstem auditory pathway during the first few months after birth, a study in Turkey demonstrated that infants fed a formula containing DHA showed more rapid brainstem auditory-evoked potentials at age 16 weeks than infants fed a formula without DHA.⁶⁵ Future studies that examine precise hypotheses related to specific nutrients, neurodevelopmental processes, timing, and brain areas are needed to clarify the relationship between nutrition and brain development and its mechanisms. For a more complete discussion of the timing of neurodevelopmental processes and implications for measurement see Georgieff⁶⁶ and Wachs et al.⁶⁷

Degree of nutrient deficiency

Much evidence shows that brain development may be compromised when nutrient deficiency is severe to moderate but spared when deficiency is mild to moderate. A number of homeostatic mechanisms protect the developing fetus and the developing brain from nutrient deficiency to a certain degree. For example, in the case of placental insufficiency, when insufficient nutrients and oxygen are available, fetal cardiac output is redistributed such that blood flow to the peripheral tissues decreases and blood flow to the brain, adrenal glands, and heart increases. This leads to brain sparing, or the sparing of brain growth even when overall fetal growth is reduced.⁶⁸ Another mechanism that protects the fetus from iron deficiency to a certain degree is the increased transfer of iron across the placenta as maternal levels decrease.⁶⁹ For each nutrient, there is likely to be a threshold at which deficiency results in impairment for the child. Exactly where this line is drawn is an important question which must be answered for each nutrient individually.

Several studies have shown that the effect of nutritional supplementation on brain development depends on initial nutritional status. For example, in Bangladesh and Indonesia, a positive effect of maternal multiple micronutrient supplementation during pregnancy and postpartum on child motor and cognitive development was found only in children of undernourished mothers.^{70,71} Similarly, in Chile, infants with low hemoglobin concentration at age 6 months showed improved cognition at age 10 years if they had been fed iron-fortified formula (compared to low-iron formula) during infancy, whereas children with high hemoglobin concentration at age 6 months performed better in cognitive tasks at age 10 years if they had received low-iron formula.⁷² In summary, greater severity of nutritional deficiency increases both the likelihood of negative effects on brain development and the likelihood of positively responding to nutritional supplementation.

Possibility of recovery

Even if the timing and the degree of nutrient deficiency are sufficient to alter brain development, one important question is whether these changes can be subsequently corrected. If not, children undernourished in early life would show permanent developmental deficits. On the other hand, if some or all of these structural alterations can be corrected, children could partly or fully recover cognitive ability.

The brain's potential for recovery from early damage has been widely studied in the context of neurological injury during development. When a certain part of the brain is damaged during early life, recovery happens in three ways, depending on the timing of the injury and subsequent experience. First, there are changes in the organization of the remaining intact circuits in the brain that were left uninjured, involving the generation of new synapses in existing pathways. Second, new circuitry that did not exist before the injury develops. Third, neurons and glia are generated to replace the injured neurons and glia.⁷³ In the case of brain alterations caused by nutrient deficiency, recovery is plausible if nutrients become available during the time that the affected growth process is still occurring. In addition to nutrient repletion, enhanced sensory, linguistic, and social interactions may also facilitate recovery.

Data from a group of Korean orphans adopted by middle-class American families provided an opportunity to investigate the possibility of recovery. Children who were undernourished at the time of adoption (before age 2 years) did not score below the normal range on IQ tests at school age, but their scores were lower than those of Korean adoptees who had not been undernourished in infancy.⁷⁴ In addition, children adopted after age 2 years had lower IQ scores than those adopted before age 2 years, suggesting that improved conditions earlier rather than later in childhood provide a greater benefit.⁷⁵

Other investigators have studied adults who were born during a period of famine in Holland during World War II when strict food rations were imposed on the entire Dutch population, including pregnant women. Children born during this period experienced nutrient deprivation *in utero* but adequate nutrition and health care thereafter. At age 19 years, their average IQ did not differ from that of a group whose mothers did not experience famine during pregnancy.⁷⁶ However, adults exposed to this famine in utero had increased risk of diagnosis of schizophrenia⁷⁷ and antisocial personality disorder,⁷⁸ as well as admittance to an addiction treatment program.⁷⁹ Together, this evidence suggests that some, but not all, of the negative effects of early undernutrition on brain development can be reversed through subsequent improvement in nutrition, health care, and enriched environments.

In these studies, the role of improved nutrition and the role of stimulation from the environment in recovery cannot be distinguished. Other evidence suggests that both of these can contribute to cognitive recovery after early undernutrition. In a large cohort of Peruvian children ($n = 1,674$), children who had been stunted before age 18 months but who were not stunted at age 4–6 years performed as well as children who had never been stunted in vocabulary and quantitative tests, while children who did not experience catch-up growth scored significantly lower.⁸⁰ In other studies, providing cognitive stimulation to children who suffered from an episode of severe acute malnutrition or IDA in early life improved mental and motor development.^{55,81} This type of evidence has led the World Health Organization to recommend structured activities to promote cognitive development as a component of the treatment of early childhood malnutrition, in addition to nutrition and healthcare.⁸²

Methodological factors

The selection of assessment tools and the age of assessment can also influence whether effects are found in nutrition studies. Global measures, such as the Bayley Scales of Infant Development (BSID) or IQ tests, are widely used but may be less sensitive to nutritional deficiency than tests of specific cognitive abilities.^{83–85} In addition, using a test created in a high-income country in a low-income country without adaptation can lead to systematic bias.^{86,87} For a more complete discussion of assessing cognitive abilities in nutrition studies, see Isaacs and Oates.⁸⁴

Detecting the effects of early nutrient deficiency can also depend on the age of cognitive assessment. For example, a group of children who experienced thiamine deficiency in infancy did not show neurological symptoms at the time of deficiency, but showed language impairment at age 5–7 years.⁸⁸ Similarly, in a randomized controlled trial, infants who received formula containing certain fatty acids (docosahexaenoic acid and arachidonic acid) showed higher vocabulary and IQ scores at age 5–6 years compared to infants who received formula without these fatty acids, even though they did not differ in vocabulary or BSID scores at age 18 months.⁸⁵ These examples show that long-term effects may be found even when immediate effects of early nutritional deficiency are not apparent.

In summary, the long-term effect of nutritional deficiency on brain development depends on the timing and degree of deficiency, as well as the quality of the child's environment. Recovery is possible with nutrient repletion during a time period when the affected neurodevelopmental process is ongoing and with enhanced interaction with caregivers and other aspects of the environment.

As shown in Table 1, research in animals has demonstrated the effects of many specific nutrient deficiencies on the development of brain structure and function. However, studies examining the effect of mild to moderate undernutrition on brain development in free-living mothers and children have largely shown mixed or inconclusive results. The factors discussed such as the timing and degree of deficiency and interactions with the amount of stimulation children receive may account for some of these mixed results. In addition, in many studies, undernutrition is confounded by other factors such as poverty, unstimulating environments, little maternal education, poor healthcare, and preterm birth, which make it difficult to isolate the effects of nutrition. To do this, randomized controlled trials are needed, but few of these specifically examining neurobehavioral outcomes have been conducted. The following sections briefly review studies of the long-term consequences of undernutrition in early life, food and protein/energy supplementation, breastfeeding practices, essential fatty acids, and certain specific micronutrients, with a focus on studies from low- and middle-income countries.

Long-term consequences of undernutrition in early life

Many studies have compared school-age children who had suffered from an episode of severe acute malnutrition in the first few years of life to matched controls or siblings who had not. These studies generally showed that those who had suffered from early malnutrition had poorer IQ levels, cognitive function, and school achievement, as well as greater behavioral problems.⁸⁹ A recent study in Barbados showed that adults who had suffered from an episode of moderate to severe malnutrition in the first year of life showed more attention problems⁹⁰ and lower social status and standard of living⁹¹ than matched controls, even after 37–43 years.

Chronic malnutrition, as measured by physical growth that is far below average for a child's age, is also associated with reduced cognitive and motor development. From the first year of life through school age, children who are short for their age (stunted) or underweight for their age score lower than their normal-sized peers (on average) in cognitive and motor tasks and in school achievement. Longitudinal studies that have followed children from infancy throughout childhood have also consistently shown that children who became stunted (height for age < -2 SD below norm values) before 2 years of age continued to show deficits in cognition and school achievement from the age of 5 years to adolescence.⁹²

Growth faltering can begin before birth, and the evidence indicates that being born small for gestational age is associated with mild to moderately low performance in school during childhood and adolescence, and with lower psychological and intellectual performance in young adulthood.⁹³ However, recent studies in low- and middle-income countries that have examined the relationship between low birth weight (<2,500 g/5.5 lb) and IQ, behavior problems, and academic achievement in school-age children, with and without controlling for gestational age at birth, have shown mixed results.⁹⁴ In a large study in Taiwan, adolescents who were born at term with low birth weight scored slightly but significantly lower than those born at term with normal birth weight on language, math, and science tests.⁹⁵ However, no effects of full-term low birth weight on IQ or behavior problems were found between the ages of 6–12 years in recent studies in Jamaica, Brazil, and South Africa.^{96–98}

As discussed earlier, certain protective factors after birth may reduce the risk of long-term effects of low birth weight, such as high socioeconomic status,⁵² cognitive stimulation in early life,⁸¹ catch-up growth in height, and increased duration of breastfeeding.⁹³ The mechanism of brain sparing, also discussed earlier, may also be a protective factor. One well-controlled study showed cognitive deficits at 7 years of age in children who had been low-birth-weight infants compared to their normal-birth-weight siblings only if head growth was also compromised.⁹⁹ Another study showed that the ratio of neonatal head circumference to birth weight (cephalization index) was a better predictor of IQ at 3 years of age (inverse association) than was birth weight (positive association).¹⁰⁰

This evidence shows that severe acute malnutrition and chronic malnutrition are clearly associated with impaired cognitive development, while the effects of growth faltering before birth are less clear and may be amenable to cognitive recovery.

Food and protein/energy supplementation

Children who experience severe acute malnutrition, chronic malnutrition, and low birth weight tend to face other disadvantages that also affect brain development, such as poverty, poor housing and sanitation, poor health-care, and less stimulating home environments, making it difficult to draw a causal link from observational studies. The results of randomized trials of maternal and child food supplementation, which provide stronger evidence of causation, are mixed (Table 2). Such trials that provided supplements to both mothers during pregnancy and children throughout the first 2 years of life showed the strongest evidence for long-term positive effects regarding cognition. In a large trial in Guatemala, pregnant women and their children up to the age of 7 years were provided

with a milk-based high protein and energy drink with micronutrients or a low protein and energy drink with micronutrients. Children who received the high protein and energy drink had higher cognitive scores at 4–5 years of age, higher scores on tests of numeracy (math), knowledge, vocabulary, and reading achievement at 11–18 years of age⁵⁴ and on reading and IQ scores (among women) at 22–29 years of age,¹⁰¹ and a 46% increase in average wages (among men) at 26–42 years of age.¹⁰² While some of the effects on school-age performance were found in the late exposure group (after the age of 2 years), most of these effects were only found among individuals who began supplementation before the age of 2 or 3 years, including the effect on average wages. In contrast, few long-term effects have been reported when supplementation was provided only to mothers or only to children, though some such trials have demonstrated short-term cognitive and motor effects (Table 2).

Apart from the trial in Guatemala, only a trial in Jamaica¹¹³ conducted longitudinal assessment at multiple time points throughout childhood and adolescence (Table 2). Although this trial did not show long-term effects of the nutrition component of the intervention, the psychosocial stimulation component resulted in sustained effects on IQ, language, and reading ability up to 18 years of age.¹¹³ The authors suggested that the lack of sustained effects of the nutrition component may have been because beginning supplementation sometime between 9 and 24 months was too late or because the supplements may not have been consumed exclusively by the children. They indicated that beginning supplementation at an earlier age or achieving higher compliance with supplement consumption may have resulted in more lasting effects.¹¹³

Together, this evidence suggests that adequate nutrition during pregnancy and throughout infancy is necessary for optimal cognitive development. However, the most effective timing for nutritional supplementation is not yet clear, since few randomized trials have been conducted and even fewer have evaluated cognition and other outcomes in adolescence and adulthood.

Breastfeeding practices

Breastfeeding may improve cognitive development through several potential mechanisms, related both to the composition of breast milk and to the experience of breastfeeding. A suite of nutrients, growth factors, and hormones that are important for brain development are abundant in breastmilk, including critical building blocks such as DHA and choline.^{115–117} Also, the physical act of breastfeeding may foster a positive mother-infant relationship and enhance mother-infant interaction, which are important for cognitive and socioemotional development. Breastfeeding also elicits a hormonal

Table 2 Randomized trials of food supplementation with micronutrients and/or balanced protein and energy to mothers and/or children and their effect on brain development.

Study location	Intervention	Age at intervention	Age at assessment	Results
New York City ¹⁰³	High protein and energy drink with increased amounts of micronutrients versus moderate protein and energy drink with standard amounts of micronutrients	Maternal supplementation throughout pregnancy until birth	12 months	No effect was found on the BSID mental or motor scores at age 12 months, but children whose mothers had received the high protein/energy drink scored higher on two information processing measures (visual habituation and dishabituation) and one of five measures of play (length of play episodes).
Taiwan ^{104,105}	High protein and energy drink with micronutrients versus no protein, low energy drink with micronutrients	Maternal supplementation throughout pregnancy and lactation	8 months 5 years	A positive effect was found on BSID motor but not mental scores. No effect on IQ or mental age (mental ability expressed in years of age by comparison with a norm reference group).
Guatemala ^{54,101,102}	High protein and energy drink with micronutrients versus no protein, low energy drink with micronutrients	Maternal and child supplementation throughout pregnancy and until age 7 years	11–18 years 22–29 years (women) 26–42 years (men)	Positive effects were found on tests of math and knowledge scores. Positive effects on vocabulary and reading achievement were found only in children who received supplementation before 2 years of age. A positive effect was found on reading and IQ scores. The high protein and energy drink resulted in a 46% increase in average wages.
Colombia ^{50,106}	Families who were provided with food (e.g., oil, dried milk, and bread) versus families who did not receive food	Throughout pregnancy and until age 3 years	3 years	A positive effect was found on Griffith's Developmental Quotient.
Indonesia ^{107,108}	Children in daycare centers who were provided with snacks containing protein and energy versus children in daycare centers not provided with snacks	Children between ages 6 and 20 months at enrollment for 3 months of intervention	5–8 years 9–23 months	A positive effect was found on reading readiness but not arithmetic or knowledge. A positive effect was found on BSID motor but not mental scores.
Indonesia ^{109,110}	High protein and energy milk plus micronutrient tablet (treatment 1) versus low protein and energy milk plus micronutrient tablet (treatment 2) versus low protein and energy milk plus placebo (control)	Children age 12 or 18 months at enrollment for 12 months of intervention	8–9 years 24 or 30 months	A positive effect was found on a test of working memory but not on reaction time, recall, emotionality, vocabulary, or arithmetic Positive effects of the two treatments versus the control were found on several measures of motor development and activity levels. An effect of the high protein and energy milk was found on one of several measures of cognitive development.
Jamaica ^{49,111–114}	Stunted children assigned to supplementation with high protein and energy milk or psychosocial stimulation or both supplementation and stimulation versus non-stunted controls	Children age 9–24 months at enrollment for 2 years of intervention	33–48 months 7–8 years 11–12 years 17–18 years	A positive effect of supplementation was found on Griffith's Developmental Quotient as well as the locomotor and performance subscales No effect of supplementation on a battery of cognitive tests No effect of supplementation on a battery of cognitive tests No effect of supplementation on cognition or mental health

Abbreviations: BSID, Bayley Scales of Infant Development.

response in mothers during each feeding session, which may reduce stress and depression and thus improve infant caregiving and mother-infant interaction.¹¹⁸

In high-income countries, children who are breastfed as infants tend to have higher IQs at school-age than children fed with formula. Meta-analyses have yielded pooled estimates of 3–5 IQ points favoring children who had been breastfed,^{119–121} with higher estimates among those born with low birth weight (5–8 IQ points).^{120,121} However, not all studies have found this positive relationship¹²² and this relationship may be confounded by other factors, since mothers from higher socioeconomic backgrounds and with higher IQs are generally more likely to breastfeed in high-income countries.^{123,124}

This problem of confounding is less likely in low- and middle-income countries. For example, among a group of mothers in the Philippines, those from the poorest environments breastfed the longest¹²⁵ and in two separate cohorts in Brazil, socioeconomic status was unrelated to breastfeeding practices.^{126,127} The study in the Philippines showed that increased duration of breastfeeding was associated with better cognitive performance at age 8–11 years.¹²⁵ The first study in Brazil demonstrated that children who were breastfed for 9 months or more were ahead by 0.5 to 0.8 school grades at age 18 years relative to those breastfed for less than 1 month.¹²⁶ The second study in Brazil showed that higher IQ scores at age 4 years were associated with increased duration of breastfeeding, with children who were breastfed for 6 months or more scoring 6 IQ points higher than those breastfed for less than 1 month. Together, these positive associations between longer duration of breastfeeding and higher IQ and school achievement, after controlling for potential confounders, support the idea that a causal relationship exists.

The strongest evidence supporting the conclusion that breastfeeding is beneficial for brain development is from a large cluster-randomized trial in Belarus.¹²⁸ Clinics were randomly assigned to a breastfeeding promotion intervention or standard healthcare. Mothers in the breastfeeding promotion group had higher rates of any breastfeeding from birth to 12 months of age and higher rates of exclusive breastfeeding when the infants were 3 months of age. At a subsequent follow-up (mean age, 6.5 years), children in the breastfeeding promotion group had higher IQ scores and higher teacher ratings of reading and writing ability. This evidence indicates that promotion of breastfeeding can be an effective strategy to improve children's cognitive development.⁵⁹

Essential fatty acids

As shown in Table 1, essential fatty acids (EFA) and their derivatives are important for membrane function,

synapse function, and myelination. Researchers have examined whether feeding infants formula containing these fatty acids positively affects cognitive development compared to standard formula that does not contain them. The authors of two recent papers, the first reporting a review¹²⁹ and the second a meta-analysis¹³⁰ of randomized controlled trials, concluded that EFA-containing formula does not affect general neurobehavioral development in full-term infants.¹³⁰ A positive effect among preterm infants, who are at risk for deficiency in certain fatty acids, including DHA, has been more frequently found.¹²⁹ Preterm infants are at risk because fatty acids accumulate rapidly in the brain during the third trimester of pregnancy.¹³¹ Preterm birth interrupts this accumulation and puts the infant at risk for deficiency. However, in the report of Qawasmi et al.,¹³⁰ the pooled effect of EFA-containing formula on development among preterm infants was not significant. Note that most of the studies included in these two papers examined the effects on BSID scores. As discussed above, a recently published study showed a positive effect of EFA-containing formula on vocabulary and IQ at the age of 5–6 years even when no effect on 18-month BSID scores was found: this suggests the latter measure may not be sensitive enough to detect effects.

Supplementary EFA may benefit children in low- and middle-income countries whose diets may be lacking in EFA. However, very little research has been conducted in these countries. Studies in Turkey, Ghana, and China suggest that supplementation with EFA may affect infant neurodevelopment⁶⁵ and motor development.^{132,133} However, other trials in Africa did not find any difference in mental or motor development, e.g., in the Gambia, when fish oil was provided from 3 to 9 months,¹³⁴ and in Malawi, when complementary foods that differed in fatty acid content were provided from 6 to 18 months.¹³⁵ In the trial in the Gambia, the lack of effect is understandable, given that the infants were not deficient in fatty acids at baseline. Similarly, the latter trial was conducted in an area near Lake Malawi, where maternal fish consumption may result in relatively high levels of key fatty acids in breast milk, possibly masking any effects of supplementary EFA.

The effect of EFA on brain development during pregnancy is also not yet clear. While fatty acids are important for fetal neurodevelopment, randomized trials of maternal EFA supplementation have yielded mixed results. Gould et al.¹³⁶ recently conducted a systematic review and meta-analysis of randomized trials of maternal DHA supplementation. The meta-analysis on cognitive, language, and motor scores revealed no differences between supplemented and control children from birth to age 12 years, except for cognitive scores in children between the ages of 2 and 5 years. The authors concluded that

methodological limitations in the 11 trials reviewed precluded confidence in the results; therefore, additional methodologically sound studies are needed, especially in children from disadvantaged or low-income backgrounds.¹³⁶

Micronutrients

Micronutrient deficiency is a critical concern for mothers and children throughout the world. It is estimated that 25% of the world's population suffers from IDA,¹³⁷ 33% have insufficient zinc intake,¹³⁸ and 30% have inadequate iodine intake.¹³⁹ Each of these micronutrients is involved in brain development (Table 1) and deficiencies are likely to impair cognitive, motor, and socioemotional abilities.

Iron. Iron is an essential structural component of the hemoglobin molecule, which transports oxygen to all the organs of the body, including the brain. IDA, that is, underproduction of hemoglobin due to iron deficiency, is a risk factor for both short-term and long-term cognitive impairment. IDA during infancy is associated with poor mental and motor development and during later childhood, with poor cognition and school achievement. Longitudinal studies have also consistently demonstrated that children who had been anemic before 2 years of age continued to show deficits in cognition and school achievement from 4 to 19 years of age.¹⁴⁰

These long-term effects of infant IDA may persist even if iron treatment is provided during infancy. In longitudinal studies, adolescents who had been iron-deficient anemic in infancy continued to score lower than their non-anemic peers in IQ, social problems, and inattention, even though they were given iron treatment as infants.¹⁴¹

Prenatal iron supplementation may prevent some of these deficits. However, among three randomized trials of maternal iron supplementation during pregnancy that measured subsequent cognitive development of the children, only one showed positive results. In that trial, which was conducted in an area of Nepal with a high prevalence of IDA, children whose mothers had received iron, folic acid, and vitamin A performed better than those whose mothers had received vitamin A alone on tests of non-verbal intelligence, executive function, and motor ability at 7–9 years of age.¹⁴² Two trials in China and Australia did not demonstrate effects of maternal iron supplementation on BSID scores at 3, 6, or 12 months of age¹⁴³ or on IQ at 4 years of age.¹⁴⁴

Provision of iron to infants in low- and middle-income countries, where rates of iron deficiency are usually high, has consistently led to improved outcomes at the end of the intervention period. These trials are

different from treatment trials in that all children are included, even if they have not been diagnosed with IDA, and the dose of iron is lower. Of five such trials, all showed positive effects on motor development, two on cognitive/language development, and three on socioemotional development.¹⁴¹ These short-term results suggest that provision of iron to populations at risk for iron deficiency could have long-lasting positive effects. However, two recent follow-up studies reported no effect of iron supplementation in infancy on motor and cognitive ability at age 3.5 years in Sweden¹⁴⁵ and 7–9 years in Nepal.^{146,147} However, the study in Sweden found a significant impact on socioemotional development. Further long-term follow-up studies that examine cognitive, motor, and socioemotional skills are needed. Importantly, the provision of iron in malaria-endemic regions should be accompanied by adequate malaria surveillance and treatment.¹⁴⁸

Taken as a whole, the evidence indicates that IDA during infancy is a strong risk factor for cognitive, motor, and socioemotional impairment in both the short and long term. Avoiding such consequences may require control of iron deficiency before it becomes severe or chronic, starting with adequate maternal iron intake before and during pregnancy and delayed cord clamping at birth.¹⁴⁹ Other elements of an appropriate strategy include preventing premature birth, feeding children iron-rich complementary foods, and providing postnatal services that promote responsive mother-infant interactions and early learning opportunities.¹⁵⁰

Iodine. Iodine is necessary for the synthesis of thyroid hormones, which are essential for central nervous system development, including neurogenesis, neuronal migration, axon and dendrite growth, synaptogenesis, and myelination (Table 1). Pregnant women with severe iodine deficiency may underproduce thyroid hormones, leading to cretinism in the child. Cretinism is a disorder characterized by mental retardation, facial deformities, deaf-mutism, and severely stunted growth. Cretinism cannot be reversed after birth but can be prevented by the correction of iodine deficiency before conception.¹⁵¹

Even in the absence of overt cretinism, the evidence suggests that chronic iodine deficiency negatively affects intelligence. A meta-analysis showed a 13.5 IQ point difference between individuals living in iodine-sufficient and iodine-deficient areas.¹⁵² Another more recent meta-analysis of studies in China indicated a similar estimated difference of 12.5 IQ points.¹⁵³ These results are equivalent to an effect size of 0.8–0.9 standard deviations. Although striking, these correlational studies may be confounded by uncontrolled factors, and randomized controlled trials of iodine supplementation in school-age children have yielded inconsistent results.¹⁵⁴

Pregnancy seems to be a sensitive period with regard to the effects of iodine deficiency on neurodevelopment, since cretinism develops during this period. In an iodine-deficient region in China, 4–7-year-old children whose mothers were given iodine during pregnancy performed better on a psychomotor test than those who were supplemented beginning at 2 years of age.¹⁵⁵ A recent study in the United Kingdom suggests that even mild iodine deficiency in the first trimester of pregnancy can negatively affect children's cognition 8 years later. Among over 1,000 8-year-old children in the UK, those whose mothers had been iodine deficient in the first trimester of pregnancy were more likely to have scores in the lowest quartile for verbal IQ and reading comprehension.¹⁵⁶ Only two small randomized controlled trials of iodine supplementation during pregnancy have examined neurobehavioral outcomes, one among 72 mothers in Peru and another among 75 mothers in the Democratic Republic of Congo.¹⁵⁷ The average effect on the IQ scores of the children in these two trials at age 0–5 years was 10.2 IQ points.¹⁵⁷ Bougma et al.¹⁵⁷ also reviewed non-randomized iodine intervention studies and cohort studies in children age 5 years and under and found average effect sizes of 6.9–8.1 IQ points. The authors concluded that additional well-designed randomized controlled trials are needed to quantify more precisely the contribution of iodine deficiency to brain development in young children, including trials examining iodized salt.¹⁵⁷

Though few well-designed controlled studies have been reported, adequate iodine intake is clearly necessary for normal brain development. Prevention of iodine deficiency, especially for pregnant mothers, is an important way to promote healthy brain development in children worldwide.

Zinc. Zinc is the fourth most abundant ion in the brain, where it contributes to brain structure and function through its role in DNA and RNA synthesis and the metabolism of protein, carbohydrates, and fat.¹⁵⁸ Although maternal and infant zinc deficiency in animals causes deficits in activity, attention, learning, and memory,¹⁵⁹ the evidence to date from human studies has not shown positive effects of zinc supplementation during pregnancy or infancy on child cognitive development.

Randomized trials of zinc supplementation during pregnancy in the United States, Peru, Nepal, and Bangladesh have shown no effects^{142,160,161} or negative effects¹⁶² of zinc compared to placebo or other micronutrients on the motor and cognitive abilities of children between the ages of 13 months and 9 years.

Similarly, infant zinc supplementation has not been demonstrated to improve cognitive development. Nine randomized controlled trials have provided zinc to infants beginning before the age of 2 years for at least 6

months and evaluated cognitive and/or motor development. Four of these provided zinc with or without iron or other micronutrients^{147,163–165} and one provided zinc with or without psychosocial stimulation.⁵⁶ Only one trial showed a positive effect of zinc on mental development and this benefit was found only in children who also received psychosocial stimulation; in the group who did not receive stimulation, there was no difference between the zinc and placebo groups.⁵⁶ One trial resulted in a negative effect of zinc supplementation on mental development compared to placebo.¹⁶⁶

In these nine trials, positive effects on motor development were more commonly found. Four of the trials showed that zinc supplementation improved motor development,^{56,164,167,168} though one of these found an effect on the motor quality rating of the Bayley Behavior Rating Scale rather than on the Bayley Motor score,¹⁶⁸ and another showed an impact of zinc only when given in combination with iron.¹⁶⁴ In this latter study, iron and zinc together and iron and zinc in combination with other micronutrients, but not iron or zinc alone, affected motor development compared to placebo (riboflavin alone). Two other trials in India and Guatemala indicated that zinc supplementation in children under 2 years of age increased activity levels.^{169,170}

The available evidence suggests that zinc supplementation during pregnancy does not seem to improve childhood cognitive or motor development. Zinc supplementation during infancy may positively affect motor development and activity levels, but it does not seem to affect early cognitive ability. A 2009 meta-analysis of randomized controlled trials of zinc supplementation in infants did not find any evidence of impact on BSID mental or motor scores; however, the authors concluded that the number of available studies is still relatively small, and the duration of supplementation in these studies may be too short to permit detection of such effects.¹⁷¹

B-vitamins. Like zinc, B-vitamins, including thiamine, are important for brain development and function through many mechanisms. They play a role in carbohydrate metabolism (which helps to provide the brain's energy supply), membrane structure and function, and synapse formation and function.¹⁷² Neurological symptoms typically characterize thiamine-deficiency disorders. In high-income countries, thiamine deficiency in infants has become a rare condition since food has been enriched with thiamine. However, recent evidence suggests that the prevalence of thiamine deficiency may be relatively high in some low-income countries. Of 778 infants who were admitted to a hospital in Laos without clinical signs of thiamine deficiency, 13.4% showed biochemical signs of thiamine deficiency based on analysis of their blood.¹⁷³

Moreover, a recent study in Israel demonstrated language deficits in 5–7-year-olds who had been fed a thiamine-deficient formula during infancy.⁸⁸ When doctors discovered that a certain manufacturer had mistakenly stopped adding thiamine to its infant formula in early 2003, they monitored the development of infants who had been fed that formula as high-risk patients. These children showed impaired language ability compared to control children at 5 years of age, even though they had not displayed any neurological symptoms during infancy.⁸⁸ The prevalence of thiamine deficiency and its effects on brain development require further research.⁵⁹

Other observational studies have demonstrated associations between infant development and maternal niacin and vitamin B₆ intake during pregnancy,¹⁷⁴ maternal riboflavin, niacin, and vitamin B₆ intake during lactation,¹⁷⁵ and infant cobalamin and folate status.¹⁷⁶ Although randomized trials of supplementation with B-vitamins alone have not been conducted, many studies of multiple micronutrient supplementation included B-vitamins, as discussed below.

Multiple micronutrients. Individuals who are deficient in one micronutrient are commonly at risk for deficiencies in others as well. Supplementation with any single micronutrient may not affect cognitive and motor development in individuals who are also deficient in other micronutrients. In these groups, supplementation with multiple micronutrients may be more beneficial than supplementation with a single micronutrient. The conversion of EFAs to DHA also depends on certain micronutrients and, thus, micronutrient deficiency may influence development through fatty acid status.¹⁷⁷

Three randomized trials have reported positive effects of multiple micronutrient supplementation during pregnancy on child development between the ages of 6 and 18 months, including motor development in Bangladesh and Tanzania^{70,178} and cognitive development in China.¹⁴³ A trial in Indonesia showed positive effects of maternal multiple micronutrient supplementation on motor and cognitive development at age 3.5 years in the children of undernourished and anemic mothers.⁷¹ In a fifth trial, 7–9-year-old children in Nepal whose mothers had received 15 micronutrients during pregnancy scored higher on a test of executive function than those whose mothers had received vitamin A alone.¹⁴² However, this benefit was found for only one of six tests of motor and cognitive function. As described above, children of mothers in this same study in Nepal who received iron, folic acid, and vitamin A scored higher than those whose mothers received vitamin A alone on five of six cognitive and motor tests.

Studies of multiple micronutrient supplementation during infancy have shown some benefits immediately

after the supplementation period. Three randomized trials in Ghana, China, and South Africa demonstrated positive effects on motor development in children between the ages of 12 and 18 months^{132,133,179} and one trial also showed an effect on the overall developmental quotient.¹³³ In Mexico, infants between the ages of 8 and 12 months who had received multiple micronutrient supplementation for 4 months were more active than those who had not received supplementation.¹⁸⁰ However, a randomized trial in Bangladesh did not show an effect on mental or motor development in infants who received 16 micronutrients compared to infants who received one or two micronutrients.¹⁶⁴ Longer-term outcomes of these trials have not yet been reported.

CONCLUSION

When a child is adequately nourished from conception through infancy, the essential energy, protein, fatty acids, and micronutrients necessary for brain development are available during this foundational period, establishing the basis for lifetime brain function. The well-nourished child is also better able to interact with his or her caregivers and environment in a way that provides the experiences necessary for optimal brain development. Children who are not adequately nourished are at risk for failing to reach their developmental potential in cognitive, motor, and socioemotional abilities. These abilities are strongly linked to academic achievement and economic productivity. Therefore, preventing or reversing developmental losses in early childhood is crucial for fostering economic development in low- and middle-income countries as well as reducing economic disparities in high-income countries.

The evidence is clear that the following conditions are key risk factors for poor motor, cognitive, and socioemotional development: severe acute malnutrition (very low weight for height), chronic undernutrition (as evidenced by intrauterine growth retardation and linear growth retardation or stunting), IDA, and iodine deficiency. Preventing these conditions should be a global health priority.

The following interventions are examples of strategies that have been found to be effective in preventing or improving these conditions: salt iodization to prevent iodine deficiency,¹⁸¹ provision of iron via home fortification (e.g., with micronutrient powders) to prevent IDA,¹⁴⁸ and educational interventions that include a strong emphasis on feeding nutrient-rich animal source foods, in conjunction with food supplementation in food-insecure populations.¹⁸² With the exception of a few studies on food supplementation (Table 2), direct evidence of the impact of these strategies on brain development is scarce.

Strategies to promote exclusive breastfeeding during the first 6 months of life and continued breastfeeding thereafter, along with adequate complementary feeding, are also likely to improve cognitive development, though additional evidence for the effectiveness of these strategies is also needed.⁹⁴

The following interventions are promising for preventing developmental loss: supplementation with iron and folic acid and/or multiple micronutrients during pregnancy, provision of multiple micronutrients (in addition to iron) during infancy, supplementation with essential fatty acids during pregnancy and infancy, fortified food supplements provided during pregnancy and infancy. However, additional robust research in low- and middle-income countries that evaluates the long-term effects of these interventions is needed.

The design and interpretation of further research should take into account the factors discussed above: the timing of nutrient deficiency or supplementation, the degree of deficiency, the possibility of recovery, and the potential for additive, interacting, or mediating effects with regard to the children's experiential input from the environment.

Interventions to improve the home environment and the quality of caregiver-infant interaction are also recommended to complement and enhance the effect of improved nutrition. These types of interventions are crucial to offset the negative effects of adverse environmental conditions (for example, poverty and low maternal education) that often coexist in populations in which undernutrition is common.

Integrated strategies targeting multiple risk factors, including nutrition, are necessary to reduce inequality and promote cognitive, motor, and socioemotional development in disadvantaged children worldwide, ensuring that all children have the opportunity to fulfill their developmental potential.

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