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Insight

Nutrition and brain development in early life

Elizabeth Prado and Kathryn Dewey

Summary of main points

1) Adequate nutrition during pregnancy and the first two years is necessary for normal brain development, laying the foundation for future cognitive and social ability, school success, and productivity.

2) Undernutrition may influence brain development both directly and indirectly.
- Nutrient deficiencies directly affect neurodevelopmental processes.
- Undernutrition affects children's experiences and behavior, which in turn influence brain development.

3) Priority should be given to the prevention of severe acute malnutrition (very low weight for height), chronic malnutrition (as evidenced by intrauterine growth retardation and linear growth retardation or stunting), iron-deficiency anemia, and iodine deficiency. There is strong evidence that they affect the developing brain and compromise long-term cognitive, motor, and socio-emotional development.

4) There is growing evidence that breastfeeding promotion, pre- and post-natal multiple micronutrient supplementation, pre- and post-natal supplementation with essential fatty acids, and fortified food supplements provided during pregnancy and to the child from 6 to 24 months of age can have beneficial effects on early child development. Few data exist on the long-term effects of these interventions.

5) An integrated approach is likely to be most effective for promoting optimal child development, i.e., interventions that combine improved nutrition with other strategies such as enhancing the home environment and the quality of caregiver-child interaction.

Adequate nutrition for pregnant mothers and infants is necessary for normal brain development. Pregnancy and infancy are important periods for the formation of the brain, laying the foundation for the development of cognitive, motor, and socio-emotional skills throughout childhood and adulthood. Children with restricted development of these skills during early life are at risk for later neuropsychological problems, poor school achievement, early school drop out, low-skilled employment, and poor care of their own children, thus contributing to the intergenerational transmission of poverty.

Many mothers and children in both low- and high-income countries are at risk for moderate undernutrition. Decreased fetal nutrition can be caused by poverty, maternal dieting, teenage pregnancy, and uterine vascular problems. Inadequate nutrition during infancy can result from poor infant feeding practices and/or the lack of physical or economic access to nutritious foods to complement breastfeeding. Many children worldwide face these conditions. For example, in 2010, 925 million people in the world experienced food insecurity,[1] and birth rates among teenage girls (age 15-19) ranged from an average of 103 per 1000 women in the lowest-income countries to 21 per 1000 women in higher-income countries.[2]

An estimated 200 million children under age five in low- and middle-income countries are at risk of failing to reach their developmental potential in cognitive, motor, and socio-emotional abilities, partly due to undernutrition[3] (see Figure 1). This technical brief reviews the evidence for the effect of undernutrition from conception through the first two years of life on brain

Figure 1. Estimated percentage of children under 5 failing to fulfill their developmental potential by country in 2004. Grantham-McGregor et al. (2007)

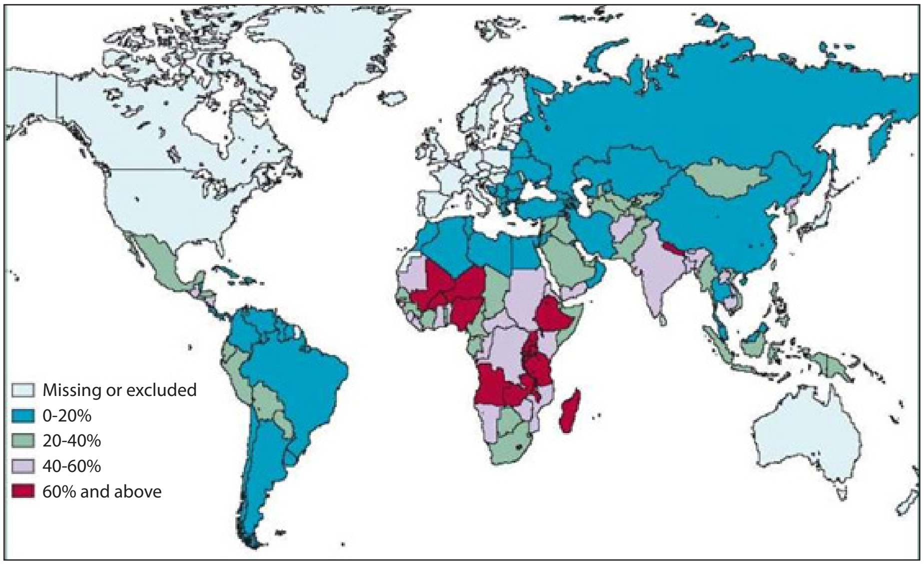
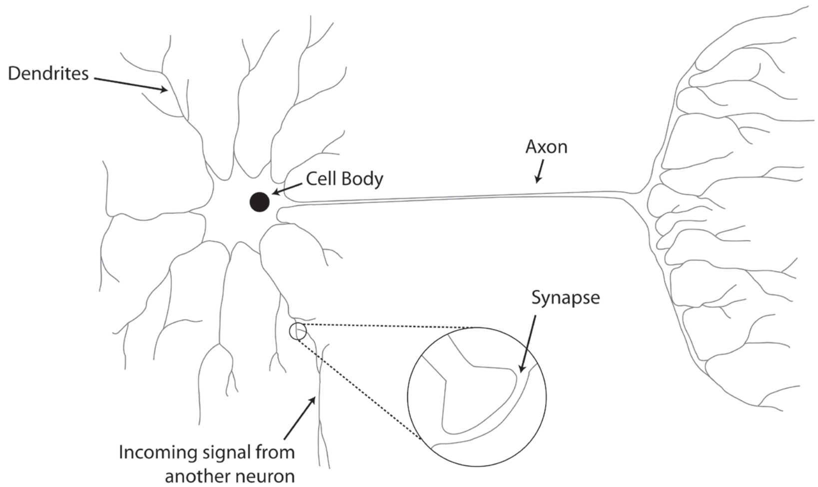


Figure 2. Structure of a neuron



Neuron: one of the cells that constitutes nervous tissue that is able to transmit and receive nervous impulses, also called a nerve cell

Axon: a long projection of the neuron that conducts nerve impulses away from the nerve cell body

Dendrite: a branching projection of the neuron that conducts nerve impulses toward the nerve cell body

Synapse: the place between nerve cells through which nerve impulses pass from one neuron to another; this process is called neurotransmission

Neurotransmitter: a substance that transmits nerve impulses across a synapse, for example, acetylcholine and dopamine

Myelin: a soft white material of lipid and protein that covers axons to insulate and accelerate nerve impulses

development and on both the short-term and long-term development of cognitive, motor, and socio-emotional skills. Appendix 1 defines these three domains of development and provides examples of tests that are commonly used to assess them in infants and older children.

Mechanisms for the effect of inadequate nutrition on brain development

Undernutrition may influence brain development by directly affecting brain processes or indirectly by affecting children's experiences and behavior. First, inadequate availability of nutrients during gestation and infancy affects the structural and functional development of the brain. Gestation and infancy are periods of rapid brain development. The neural tube begins to form 16 days after conception and within 7 months takes on a form that resembles the adult brain.[4]

Nutrients are required for many of the biological processes that drive this transformation. For example, they are needed for the creation of new neurons. A neuron

Box 1. Brain development and the child's experiences and environment

The brain develops its structural form and functional capacity through dynamic bi-directional influences between biological factors (such as nutrition), genetic factors, the child's experiences, and the child's own behavior.

Experience can affect brain development in at least two ways. Certain developmental processes have been called "experience-expectant" because the brain relies on them for normal development.[104] For example, the brain expects visual input through the optic nerve for the normal development of the visual cortex.[104]

The absence of these expected experiences impairs the neurodevelopmental processes that depend on them. These "experience-expectant" processes have been distinguished from "experience-dependent" processes.[104] The latter refers to the way the brain develops in response to an individual's experiences and acquired skills. For example, a neuroimaging study demonstrated that the rear hippocampus, a part of the brain that underlies spatial memory, was larger in London taxi drivers than age-matched comparison subjects, presumably due to their memory of the complex layout of the London city streets.[105]

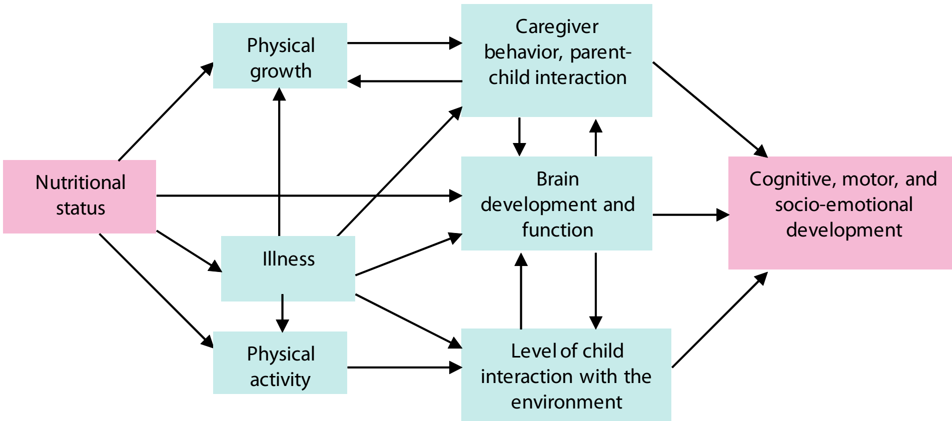
These experience-dependant processes enable individuals to adapt to and thrive in their specific culture and environment. Whereas experience-expectant processes are more likely to occur early in life, experience-dependent processes continue throughout life, suggesting that neuronal connections can re-organize in response to experiences and that new neuronal growth beyond infancy is possible.

The effects of undernutrition must be understood in the context of these multiple biological and environmental influences as well as the interactions between them. For example, low birth weight infants born into families with high socio-economic status are at lower risk for poor developmental outcomes than those born into disadvantaged environments.[19] Thus, protective environmental factors can, in some cases, buffer the potential negative effects of undernutrition. Conversely, undernourished children from disadvantaged homes where protective factors are lacking may show more response to nutrition (and other forms of) interventions.

Moreover, several studies have found that nutrition and psychosocial stimulation together result in greater improvements in child development than either intervention alone.[106]

Figure 3. Potential mechanisms for the effect of nutrient deficiency on children's cognitive, motor, and socio-emotional development

Adapted from Levitsky & Barnes (1972) and Pollitt (1993)



is pictured in Figure 2. Nutrients are also needed for the growth of axons and dendrites (also see Figure 2), the formation of synapses, and the covering of axons with myelin, which is fatty matter that accelerates the speed of nerve impulses traveling from one cell to another. Inadequate availability of energy, protein, fatty acids, and micronutrients impairs these neurodevelopmental processes.[5] These nutrients are also important for brain function throughout childhood and adulthood, for example, for the maintenance of brain tissue and for neurotransmitter synthesis.[6, 7] Most of the evidence for these direct effects on the brain comes from animal models of nutrient deficiency. A recent paper reported that moderate (30%) reduction in maternal food intake during the first half of pregnancy in baboons negatively affected fetal brain development even though fetal weight was not affected and maternal weight was only slightly affected. This suggests that the brain can be affected by moderate undernutrition during this period even in the absence of overt signs of undernutrition.[8]

Second, nutrition may affect brain development indirectly through influencing children's experiences. Children's experiences and environment are critical factors in the development of the brain and the development of cognitive, motor, and socio-emotional abilities (see Box 1). Undernutrition affects physical growth, motor development, and physical activity, which in turn may influence brain development through both caregiver behavior and child interaction with the environment[9] (see Figure 3). That is, caregivers may treat children who are small for their age as younger than they actually are, which would result in less appropriate stimulation and therefore altered brain development in an undernourished child. Undernourished children may also be frequently ill and therefore fussy, irritable, and withdrawn. This could also lead caregivers to treat them more negatively than they would treat a happy, healthy child. Additionally, lower activity levels would limit the undernourished child's exploration of the environment and initiation of caregiver interactions, which could also lead to poor brain development. Some evidence suggests that these mechanisms may contribute to delayed motor and cognitive development in infants and children with protein-energy malnutrition[10] and iron-deficiency anemia.[11, 12]

An implication of the model presented in Figure 3 is that interventions targeting both the child and the caregiver can operate at multiple levels.[13] For example, an intervention that improves the child's nutrient intake may improve the child's physical growth, activity levels, and behavior. This would then enable the child to elicit and receive age-appropriate care and positive interaction from the caregiver and improve cognitive development. On the other hand, an intervention that improves the caregiver's sensitivity and appropriate response to children's cues, for example for hunger and satiety, may improve the nutritional status of the child. This would feed back into the child's behavior and ability to elicit appropriate interaction from the caregiver. Thus, interventions aimed at either the child or the caregiver may have cumulative and cascading effects over time.

Long-term consequences of undernutrition in early life

Severe acute malnutrition (low weight for height) in early life can have long-lasting consequences on brain development even after nutritional rehabilitation. 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 found that those who had suffered from early malnutrition had poorer IQ levels, cognitive function, and school achievement, as well as greater behavioral problems.[14] To treat malnourished children, WHO recommends providing structured activities to promote cognitive development in addition to nutrition and health care. Two studies in Uganda and Bangladesh have shown that providing such stimulation can help improve mental and motor development in severely malnourished infants.[15]

Chronic malnutrition, as measured by poor physical growth, 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 perform more poorly than their normal-sized peers (on average) in cognitive and motor tasks and in school achievement.[16] Longitudinal studies have also consistently shown that children who had been stunted (height for age < -2 SD below norm values) in the first 2 years of life continued to show deficits in cognition and school achievement from age 5 years to adolescence.[16] Thus, chronic undernutrition in early life seems to have long-lasting consequences for brain development.

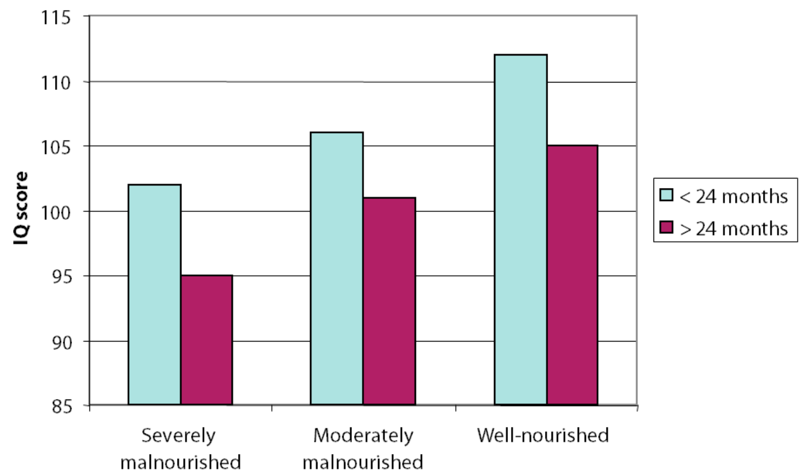
Growth faltering can begin before birth, and the evidence indicates that being born small for gestational age is associated with mild to moderately low performance in school during childhood and adolescence, and with lower psychological and intellectual performance in young adulthood.[17] However, studies that have examined the relationship between low birth weight (< 2500 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.[18] The inconsistency in findings may be explained by certain protective factors that reduce the risk of long-term effects, such as high socio-economic status,[19] cognitive stimulation in early life,[15] catch-up growth in height, and increased duration of breastfeeding.[17]

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.

Are the consequences of undernutrition irreversible?

Some, but not all, of the negative effects of early undernutrition on cognitive development appear to be reversible through subsequent improvement in nutrition, health care, and enriched environments. Korean orphans who were undernourished when they were admitted to an adoption agency (before age 2 years) and were then adopted by middle-class American families did not score below the normal range on IQ tests at school age.[20] However, they did score lower than Korean adoptees who had not been undernourished in infancy (Figure 4). In addition, those adopted before age 2 years had higher IQ scores than those adopted after age 2 years, suggesting that improved conditions before age 2 years provide a greater benefit.[21]

Figure 4. School-age IQ scores of female Korean orphans adopted into American families vary by history of malnutrition at adoption and age of adoption



Malnutrition was defined based on a reference standard of normal Korean children of the same age, with "severely malnourished" defined as below the 3rd percentile for both height and weight, and "moderately malnourished" from the 3rd through the 24th percentile. An IQ score of 100 represents the average score for a given age group in a norm reference sample. A score of 85 is one standard deviation below the mean and 115 is one standard deviation above the mean. Adapted from Winick (1975) and Lien (1977).

Other studies have examined the long-term consequences of pre-natal nutritional deprivation in Holland during World War II. During the war, strict food rations were imposed on the entire Dutch population, including pregnant women. Children born to these women experienced nutrient deprivation during gestation but adequate nutrition and health care for most of their lives. When these children were tested at age 19 for an army entrance exam, their IQ did not differ from those whose mothers did not experience famine.[22] However, pre-natal exposure to this famine increased the risk of diagnosis of schizophrenia[23] and anti-social personality disorder,[24] as well as admittance to an addiction treatment program,[25] suggesting long term impacts on neurological development.

Effects of food supplementation on brain development

Food supplementation programs and food voucher programs for low-income families have been found to improve children's IQ, behavior, and school performance. Several studies have evaluated such programs by comparing a child born while the mother participated in the program to a sibling born before participation. These studies demonstrated a benefit on school achievement in Canada,[26] higher IQ, higher estimated learning potential, and fewer behavior problems at age 6 to 8 years in the U.S.,[27] and higher IQ and school achievement in the first year of school in Mexico.[28]

Although these sibling studies suggest benefits of food supplementation in early life, the results of randomized trials of maternal and child food supplementation are mixed (Appendix 2). 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 benefits to cognition. In a large trial in Guatemala, pregnant women and their children up to age 7 were provided with a high protein and calorie drink with micronutrients or a low protein and calorie drink with micronutrients. Children who received the high protein and calorie 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 age[10] and on reading and IQ scores (among women) at 22-29 years of age.[29] Boys who received the high protein and calorie drink had a 46% increase in average wages at 26-42 years of age.[30]

In contrast, few long-term benefits 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 benefits (see Appendix 2). This evidence suggests that adequate nutrition during pregnancy and throughout early childhood 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.

Apart from the trial in Guatemala, longitudinal follow-up at multiple time points throughout childhood and adolescence has been conducted only in the trial in Jamaica (Appendix 2). Although this trial did not find long-term effects of the nutrition component of the intervention, early childhood psychosocial stimulation resulted in sustained benefits on IQ, language, and reading ability at age 18 years.[31] The authors suggested that the lack of sustained effects of the nutrition component may be because beginning supplementation at age 9-24 months was not early enough or because the supplements may not have been consumed solely by the children. They propose that beginning supplementation at an earlier age or higher compliance in consuming the supplement may have imparted lasting benefits.[31]

Breastfeeding practices

The potential mechanisms through which breastfeeding may improve cognitive development relate both to the composition of breastmilk and to the experience of breastfeeding. Breastmilk contains a suite of nutrients, growth factors, and hormones that are important for brain development, including critical building blocks such as docosahexaenoic acid (DHA) and choline.[45, 46] In addition, the physical act of breastfeeding may promote the quality of the mother-infant relationship and enhance mother-infant interaction, which are important for cognitive and socio-emotional development. Breastfeeding also elicits a beneficial hormonal response in mothers, which may reduce stress and depression and thus improve infant caregiving and mother-infant interaction.[45]

In high-income countries, school-age children who were breastfed as infants tend to have higher IQs than children who were fed with formula. Meta-analyses have reported pooled estimates of three to five IQ points favoring children who had been breastfed,[47-49] with higher estimates in low birth weight infants (five to eight IQ points).[48, 49] However, this relationship may be confounded by other factors, since mothers from higher socio-economic backgrounds and with higher IQs are generally more likely to breastfeed in high-income countries.[50, 51]

In low- and middle-income countries, this problem of confounding is less likely. For example, in a study in the Philippines, mothers from the poorest environments breastfed the longest[52] and in Brazil, socio-economic status was unrelated to breastfeeding practices in two separate cohorts.[53, 54] These three studies all showed that after controlling for potential confounders, longer duration of breastfeeding was related to higher IQ and school achievement, supporting the idea that this is a causal relationship.

The results of a recent large cluster-randomized trial in Belarus provide the strongest support for the conclusion that breastfeeding is beneficial for brain development.[55] Clinics were randomly assigned to breastfeeding promotion or standard health care. The breastfeeding promotion group had higher rates of exclusive breastfeeding when the infants were 3 months of age and higher rates of any breastfeeding from birth to 12 months of age. At 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 supports the promotion of breastfeeding as an effective strategy to improve children's cognitive development.

Essential Fatty Acids

Essential fatty acids (EFA) and their derivatives, including docosahexaeonic acid (DHA) and arachidonic acid (AA), are part of the structure of brain tissue, including cell membranes.[56] EFAs are fatty acids that are necessary for biological processes but cannot be synthesized by the body and must be obtained through the diet. Studies in animals and humans have shown that inadequate intake of DHA and AA affects their levels in the brain and the membrane activity that depends on them.[56] Researchers have examined whether formula containing these fatty acids benefits infant cognitive development compared to standard formula that does not contain them. The authors of a recent review of randomized controlled trials concluded that EFA-containing formula does not benefit general neurobehavioral development in full-term infants.[57] However, the evidence shows that there is a positive effect among pre-term infants, who are at risk for deficiency in certain fatty acids, including DHA.[57]

Since EFA-containing formula benefits pre-term infants who are at risk for deficiency, supplementary EFA may also 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 benefit infant neurodevelopment[58] and motor development.[59, 60] However, another randomized trial in Malawi did not find any difference in 18-month mental or motor development when complementary foods that differed in fatty acid content were provided.[61] This latter trial was conducted in an area near Lake Malawi, where fish consumption may result in relatively high levels of key fatty acids in breastmilk, possibly masking effects of supplementary EFA.

The effect of EFA on brain development during pregnancy is also not yet clear. Fatty acids are important for fetal neurodevelopment; however, randomized trials of maternal EFA supplementation have yielded mixed results.[57] Differences between studies in the dose and source of EFA and in initial fatty acid status of the mothers may partly account for these mixed findings. In addition, the authors of a recent review pointed out that many of these trials included a small number of children or showed high rates of attrition, making it difficult to have a high degree of confidence in the results. The authors concluded that more high quality research is needed, especially in children from disadvantaged or low-income backgrounds.[57]

Micronutrients

Micronutrient deficiency is a critical concern for mothers and children throughout the world. An estimated 25% of the world's population suffer from iron deficiency anemia,[62] 33% have insufficient zinc intake,[63] and 30% have inadequate iodine intake.[64] Each of these micronutrients is involved in brain development, and deficiencies are likely to impair cognitive, motor, and socio-emotional abilities.

Iron

Iron is an essential structural component of the hemoglobin molecule, which transports oxygen from the lungs to the rest of the body. Infants with iron-deficiency anemia, that is, underproduction of hemoglobin due to iron deficiency, are clearly at risk for both short-term and long-term cognitive impairment. Iron-deficiency anemia is associated with poor mental and motor development in infancy and poor cognition and school achievement in later childhood. Longitudinal studies have also consistently demonstrated that children who had been anemic in the first 2 years of life continued to show deficits in cognition and school achievement from 4 to 19 years of age.[65]

When a child is adequately nourished during gestation and infancy, the essential energy, protein, fatty acids, and micronutrients necessary for brain development are available during this crucial period, laying a foundation for lifetime brain function.

These long-term effects of infant iron-deficiency anemia appear to persist despite treatment with iron. Longitudinal studies have shown that children who had been iron-deficient anemic in infancy continued to show deficits in IQ, social problems, and inattention in adolescence even though they were given iron treatment in infancy.[66]

Maternal iron supplementation during pregnancy may prevent some of these deficits. However, randomized trials of maternal iron supplementation have provided inconsistent results on subsequent cognitive development of the children. Two randomized trials in China and Australia failed to show effects of maternal iron supplementation on Bayley Scales of Infant Development (BSID) scores at 3, 6, or 12 months of age[67] or on IQ at 4 years of age.[68] However, another randomized trial in an area in Nepal with a high prevalence of iron deficiency anemia indicated that 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 to 9 years of age.[69]

Provision of iron to infants in low- and middle-income countries, where rates of iron deficiency are usually high, has consistently led to improved developmental outcomes at the end of the intervention period. These trials are different from treatment trials because they include all children, whether or not they are iron deficient or anemic, and the dose of iron is lower. Out of five such trials, all showed effects on motor development, three resulted in improved socio-emotional development, and two demonstrated enhanced cognitive/language development.[66] These short-term results suggest that provision of iron to populations at risk for iron deficiency could have long-lasting positive effects, but longer-term outcomes of these studies have not yet been reported.

Taken as a whole, the evidence indicates that iron deficiency anemia during infancy is a strong risk factor for both short-term and long-term cognitive, motor, and socio-emotional impairment, and that avoiding such consequences may require control of iron deficiency before it becomes severe or chronic, starting with adequate maternal iron intake during pregnancy and delayed cord clamping at birth.[71] Other elements of an appropriate strategy include preventing premature birth, providing iron-rich complementary foods, and ensuring access to postnatal interventions that promote responsive mother-infant interactions and early learning opportunities.[72]

Iodine

Iodine is necessary for the synthesis of thyroid hormones, which are essential for central nervous system development. Severe iodine deficiency before and during pregnancy can lead to underproduction of thyroid hormones in the mother and to cretinism in the child. Cretinism is a disorder characterized by mental retardation, deaf-mutism, facial deformities, and severely stunted growth. Cretinism can be prevented by the correction of iodine deficiency before conception.[73]

Even in the absence of overt cretinism, the evidence is strong 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.[74] Another more recent meta-analysis of studies in China indicated a similar estimate of 12.5 IQ points.[75]

Pregnancy seems to be a period sensitive to the effects of iodine deficiency on neurodevelopment. Controlled trials in which mothers were injected with iodine or placebo before or during pregnancy in areas where iodine deficiency was prevalent showed benefits on infant cognitive development in the Democratic Republic of Congo[76] and motor ability at age 10-11 years in Papua New Guinea.[77] In an iodine-deficient region in China, 4- to 7-year-old children whose mothers were given iodine during pregnancy performed better on a psychomotor test than those who were supplemented beginning at age 2 years.[78]

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 necessary for many biological processes that affect brain development, including DNA and RNA synthesis and the metabolism of protein, carbohydrates, and fat. Zinc is the fourth most abundant ion in the brain, where it contributes to brain structure and function through its role in binding proteins.[79] Although animal models have shown that maternal and infant zinc deficiency causes deficits in activity, attention, learning and memory,[80] the evidence to date in humans has not shown benefits of zinc supplementation during pregnancy or infancy on child cognitive development.

Randomized trials of zinc supplementation during pregnancy in the U.S., Peru, and Bangladesh have shown no effects[81, 82] or slightly negative effects[83] of zinc compared to placebo on child motor and cognitive abilities from age 13 months to 5 years.

Similarly, infant zinc supplementation has not been demonstrated to improve cognitive development. Eight randomized controlled trials that provided zinc to infants beginning before age 2 years for at least 6 months evaluated cognitive and/or motor development. Three of these provided zinc with or without iron or other micronutrients[84-86] and one provided zinc with or without psychosocial stimulation.[87] Only one trial showed a benefit of zinc on mental development and this benefit was found only in children who also received psychosocial stimulation. In the group that did not receive stimulation, there was no difference between zinc and placebo.[87] One trial indicated a slightly negative effect of zinc supplementation on mental development compared to placebo.[88]

In these eight trials, positive effects on motor development were more commonly found. Four of the trials showed that zinc supplementation improved motor development,[85, 87, 89, 90] though one of them showed an effect of zinc only when given in combination with iron.[85] In this latter study, iron and zinc together and iron and zinc in combination with other micronutrients, but not iron or zinc alone, benefited motor development compared to placebo (riboflavin alone). Two other trials in India and Guatemala indicated that zinc supplementation in children under age 2 increased activity levels.[91, 92] The available evidence suggests that zinc supplementation during pregnancy does not seem to improve cognitive or motor development during the first few years of life. Zinc supplementation during infancy may benefit motor development and activity levels but does not seem to affect early cognitive ability. However, long-term follow up of these trial cohorts, which has not yet been conducted, may demonstrate positive effects at later ages. Effects in early childhood may be difficult to detect because there is a wide range for normal cognitive development during the early years, making scores in the first 2 years of life poor predictors of later ability and achievement.[93]

Thiamine

Like zinc, thiamine is important for brain development and function through many mechanisms, including its role in carbohydrate metabolism (which helps to provide the brain's energy supply), membrane structure and function, and synapse formation and function.[94] Thiamine-deficiency disorders are typically characterized by neurological symptoms. Thiamine deficiency in infants has become a rare condition in high-income countries where food has been enriched with thiamine. In some low-income countries, recent evidence suggests that the prevalence of thiamine deficiency may be relatively high. Out of 778 infants without clinical signs of thiamine deficiency who were admitted to a hospital in Laos during one year, 13.4% of them showed biochemical signs of thiamine deficiency based on analysis of their blood.[95]

A recent study in Israel demonstrated deficits in language abilities in 5-7 year olds who had been fed a thiamine-deficient formula during infancy.[96] When doctors discovered that a manufacturer had mistakenly stopped adding thiamine to its infant formula in early 2003, they followed up infants who had been fed that formula as high-risk patients and monitored their development. Five years later, these children showed impaired language ability compared to control children, even though they had not displayed any neurological symptoms during infancy.[96] Together, these studies suggest that thiamine deficiency and its effects on brain development may affect many children without being detected.

Multiple micronutrients
Individuals who are deficient in one micronutrient are often at risk for deficiencies in others as well. Supplementation with any single micronutrient may not benefit cognitive and motor development if deficiencies in other micronutrients are also present. Thus, supplementation with multiple micronutrients may be more beneficial than supplementation with a single micronutrient alone. Some micronutrients are also needed for the conversion of EFAs to DHA and thus may influence development through this mechanism.[97]

Three randomized trials have reported effects of multiple micronutrient supplementation during pregnancy on child development at age 6-18 months, including cognitive development in China[67] and motor development in Bangladesh and Tanzania.[98, 99] In a fourth 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.[69] 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. Thus, the long-term cognitive effects of maternal multiple micronutrient supplementation are not yet clear.

Studies of infant multiple micronutrient supplementation have shown some benefits immediately after the supplementation period. Three randomized trials in Ghana, China, and South Africa demonstrated benefits on motor development at age 12-18 months[59, 60, 100] and one trial also showed a benefit on overall developmental quotient.[60] In Mexico, infants age 8-12 months who had received four months of multiple micronutrient supplementation were more active than those who had not received supplementation.[101] However, a randomized trial in Bangladesh did not find a mental or motor advantage in infants who received 16 micronutrients compared to infants who received one or two micronutrients.[85] Longer term outcomes of these trials have not yet been reported.

Conclusions and program implications

When a child is adequately nourished during gestation and infancy, the essential energy, protein, fatty acids, and micronutrients necessary for brain development are available during this crucial period, laying a foundation for lifetime brain function. That child is also more likely to interact with his or her caregivers and environment in a way that provides the experiences necessary for optimal brain development.

Children who do not receive adequate nutrition are at risk for failing to reach their developmental potential in cognitive, motor, and socio-emotional abilities. The development of these abilities is linked to academic achievement and economic productivity. Therefore, preventing or reversing this loss 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 cognitive, motor, and socio-emotional development. Preventing these conditions should be a global health priority.

- Severe acute malnutrition (low weight for height)
- Chronic undernutrition (as evidenced by intra-uterine growth retardation and linear growth retardation or stunting)
- Iron-deficiency anemia
- Iodine deficiency

The following interventions are examples of strategies that have been found to be effective in preventing or improving some of these conditions.

- Salt iodization to prevent iodine deficiency[102]
- Provision of iron via home fortification, such as micronutrient powders, to prevent iron deficiency anemia[70]
- Educational interventions that include a strong emphasis on feeding nutrient-rich animal source foods, in conjunction with food supplementation in food-insecure populations[103]

In addition, effective strategies to promote exclusive breastfeeding during the first 6 months of life and continued breastfeeding thereafter (along with adequate complementary feeding) are likely to improve cognitive development.[18]

The following interventions are promising for preventing developmental loss. However, additional robust research in low- and middle-income countries that evaluates the long-term effects of these interventions is needed.

- 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

Strategies to improve the home environment and the quality of caregiver-infant interaction are also recommended to complement and enhance the effect of nutrition interventions and to address the negative effects of adverse environmental conditions (for example, poverty and low maternal education) that often co-exist in populations where undernutrition is common.

All children should have the opportunity to fulfill their developmental potential. Integrated interventions targeting multiple risk factors, including nutrition, are necessary to reduce inequality and promote cognitive, motor, and socio-emotional development in disadvantaged children worldwide.

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Appendix 1

Methods for the assessment of cognitive, motor, and socio-emotional abilities, and the quality of the home environment

Nutrition studies in humans rarely examine effects on measures of neural structure and function. Rather, most studies have used performance-based tests to evaluate children's cognitive, motor, and socio-emotional abilities. Performance on these tests has been linked to brain development and function in several ways. In adults, neurological and neuroimaging techniques allow inferences to be made concerning the brain areas necessary to perform specific cognitive tasks. These types of studies have clarified the brain areas underlying motor control, emotional regulation, general intellectual ability, and many other specific cognitive functions.[107] How specific brain systems and general intellectual ability develop during infancy and childhood is not yet clear. Developmental neuroscientists hold various views concerning the neural basis of changes in behavioral abilities during infancy.

Cognitive development refers to the development of perception, memory, language, concepts, spatial ability, problem-solving, reasoning and other cognitive skills. In infants, cognitive development has been commonly assessed using the second edition of the **Bayley Scales of Infant Development**-(BSID-II) Mental Scale[109] or the revised third edition, **Cognitive and Language Scales** (Bayley III).[110] These tests evaluate whether the child can perform skills such as searching for an object hidden behind a cloth, identifying objects, and responding to his or her own name.

Information processing measures, such as the **Fagan Test of Infant Intelligence**,[111] have also been used in nutrition research. In this test, the infant is presented with two identical visual stimuli for a period of time. Subsequently, the infant is presented with a previously-viewed stimulus paired with a novel stimulus. An observer records the amount of time the infant looks at each stimulus. Since infants are likely to show more interest in a novel stimulus, a greater proportion of time looking at the novel stimulus is an indication that the infant remembers and has retained information from the previously-viewed stimulus. Performance on this type of test in the first year of life has been found to predict IQ in later childhood (age 3 to 8 years).[112]

In pre-school age children (3 to 5 years), the **Wechsler Preschool and Primary Scale of Intelligence**[113] is commonly used to assess cognitive ability. In school-age children, commonly used tests are the **Wechsler Intelligence Scale for Children** (WISC)[114], **Peabody Picture Vocabulary Test** (PPVT),[115] and **Raven's Progressive Matrices**.[116] In the WISC, children are asked to perform tasks such as defining words, copying patterns using colored blocks, and repeating a sequence of digits. In each item of the PPVT, children are presented with four pictures and asked to identify the word spoken by the tester. In the Raven's Progressive Matrices, children are asked to complete a series of diagrams by analogy to a presented diagram series.

Motor development refers to the development of control and coordination of the muscles of the body. Gross motor development refers to the development of control over the large muscles of the body, such as the arms and legs. Fine motor development refers to the development of control over the small muscles of the body, such as the hands and fingers. Commonly used tests to assess motor development in infancy include the **WHO motor milestones**[117], the **Bayley III Motor Scale**, and the **Griffiths Mental Development Scale Locomotor Scale** (gross motor) and **Eye/Hand Coordination Scale** (fine motor).[118] Items assessing gross motor development include skills such as standing and walking, while fine motor items include skills such as grasping a dangling ring and using the pads of the fingers to grasp a pellet. In pre-school and school-age children the **Movement Assessment Battery for Children** (MABC) and the Purdue Pegboard test are commonly used. The MABC assesses manual dexterity, ball skills, and static and dynamic balance. The **Purdue Pegboard** test assesses the speed and dexterity with which a child can place pegs into small holes on a board.

Socio-emotional development refers to the development of emotional regulation and social competence, that is, effectiveness in social interaction with others. In infants, commonly used tests are the BSID-II Behavior Rating Scale[109] or its replacement in the Bayley III, the Socio-Emotional Scale.[110] The **Behavior Rating Scale** includes three subscales: (1) the orientation/engagement subscale, which measures the child's attention, arousal, and behavior toward the testing materials, (2) the emotional regulation subscale, which measures the child's range of affect and emotional response to both success and failure on the assessment, and (3) the motor quality subscale, which measures the quality of the child's movements, including tone and control. The **Bayley III Socio-Emotional Scale** examines six areas: (1) growing self-regulation and interest in the world, (2) engaging in relationships, (3) using emotions in an interactive purposeful manner, (4) using interactive emotional signals to communicate and solve problems, (5) using symbols to convey intentions or feelings and express more than basic needs, and (6) creating logical bridges between emotions and ideas. In pre-school and school-age children, the **Child Behavior Checklist**[119] is commonly used. Eight scores are derived from this checklist: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior.

To measure the amount and quality of stimulation that children receive from their environment, researchers have most commonly used the **Home Observation for the Measurement of the Environment (HOME) Inventory**.[120] UNICEF has recently developed a measure of the environment for its Multiple Indicator Cluster Survey (MICS), which requires less time and expertise to administer than the HOME Inventory. It consists of questions concerning activities household members do with children and the presence of learning materials in the home.[121]

Appendix 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

Location	Intervention	Age of intervention	Age of assessment	Results
New York City[32]	High protein and calorie drink with increased amounts of micronutrients versus moderate protein and calorie drink with standard amounts of micronutrients	Maternal supplementation throughout pregnancy until birth	12 months	No effect on the Bayley Scales of Infant Development (BSID) mental or motor scores at age 12 months but children whose mothers had received the high protein/calorie drink scored higher on two information processing measures (visual habituation and dishabituation) and one of five measures of play (length of play episodes).
Taiwan[33,34]	High protein and calorie drink with micronutrients versus no protein low calorie drink with micronutrients	Maternal supplementation throughout pregnancy and lactation	8 months 5 years	Effect on BSID motor but not on mental scores. No effect on IQ or mental age (mental ability expressed in years of age by comparison with a norm reference group).
Guatemala[10, 29, 30]	High protein and calorie drink with micronutrients versus no protein low calorie 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)	Effect on tests of numeracy, knowledge, vocabulary, and reading achievement. Effect on reading and IQ scores. The high protein and calorie drink resulted in a 46% increase in average wages.
Colombia[35, 36]	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 5-8 years	Effect on Griffith's Developmental Quotient. Effect on reading readiness but not on arithmetic or knowledge.
Indonesia[37, 38]	Children in daycare centers who were provided with snacks containing protein and calories versus children in daycare centers not provided with snacks	Children age 6 to 20 months at enrollment for 3 months of intervention	9 to 23 months 8-9 years	An effect was found on BSID motor but not on mental scores. An effect was found on a test of working memory but not on reaction time, recall, emotionality, vocabulary, or arithmetic.
Indonesia[39, 40]	High protein and calorie milk plus micronutrient tablet (treatment 1) versus low protein and calorie milk plus micronutrient tablet (treatment 2) versus low protein and calorie milk plus placebo (control)	Children age 12 or 18 months at enrollment for 12 months of intervention	24 or 30 months	Effects of the two treatments versus the control on several measures of motor development and activity levels. Effect of the high protein and calorie milk on one of several measures of cognitive development.
Jamaica[31, 41-43, 44]	Stunted children assigned to supplementation with high protein and calorie 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	Effect of supplementation on Griffith's Developmental Quotient and 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.

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Headquarters Office
1825 Connecticut Avenue, NW
Washington, DC 20009
United States
Tel: (202) 884-8000
Fax: (202) 464-3966
Email: aliveandthrive@fhi360.org