# Neurodevelopment: The Impact of Nutrition and Inflammation During Infancy in Low-Resource Settings

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abstract

Infancy and early childhood (ie, birth through age 24 months) represent a period of life with both exquisite opportunity and vulnerability for neurodevelopment. This is due to rapid brain development, both anatomic and functional, as well as to high nutrient requirements during a time of dependence on human milk and complementary foods. Complex interactions exist among nutrition, social, and physical environments and exposures. The newborn brain also reflects maternal exposures that occurred as the product of many interacting forces during gestation. Connections between nutrient use and acute and chronic inflammation are increasingly recognized, but the evidence base linking both nutrition and inflammation to neurodevelopment is relatively modest and quite limited for this young age group specifically. This article provides an overview of key interactions of nutritional requirements relevant to brain development and function; nutritional vulnerabilities related to maternal nutritional status and function; and the impact of environmental exposures and inflammation on nutrient homeostasis and neurodevelopment during this critical developmental window.

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Estimates of the burden of neurodevelopmental impairments in low- and middle-income countries (LMIC) are limited and highly variable, but are generally reported to be higher than in high-resource settings. In all settings, the prevalence of mild impairments is higher than severe disability.[1,2] Among several factors identified as contributors to developmental disabilities in LMIC, infections and malnutrition, including micronutrient deficiencies, are particularly important and potentially modifiable.[3]

Infancy and early childhood (ie, birth through age 24 months) represent a period of life with both exquisite opportunity and vulnerability for neurodevelopment. Not only are many aspects of brain development undergoing rapid anatomic and functional expansion during this postnatal component of the "1000 days critical window," but nutrient requirements are also high due to rapid physical growth and maturation. The complex interactions that exist among nutritional status (deficits and surfeits) as well as the social and physical environments and exposures they entail are particularly potent during this period of rapid change. Furthermore, the interactions are bidirectional, such that the developing infant not only responds to his/her environment but also, in ideal circumstances, elicits responses from adult care providers that additionally stimulate more inputs. The newborn brain also reflects maternal exposures that occurred as the product of many interacting forces during gestation.

The connections between nutrient use (absorption, excretion, and retention) and acute and chronic inflammation and stress are increasingly recognized.[4] Recent reviews have addressed selected aspects of this sensitive period, but the evidence base linking both nutrition and inflammation to neurodevelopment is only modest and even more limited for this young age group specifically. This article in the supplement will provide an overview of key aspects of interactions that are particularly relevant to the infant and young child during this critical developmental stage. The underlying framework reflecting these interrelationships and the issues particular to infants in low-resource settings (LRS) are depicted in Fig 1. Furthermore, emphasis will be placed on these sectors as they exist in, and are impacted by, environments in LRS. To advance the field, knowledge gaps and research priorities will be highlighted.

## KEY NEURODEVELOPMENTAL CONSIDERATIONS DURING INFANCY

The concept of neurodevelopment for the infant and young child includes multiple behavioral domains: motor, mental, sensory, and socioemotional. It is important to understand that these behaviors are the expression of the brain's activity. Thus, understanding brain development and the roles that nutrients and inflammation play in shaping its development and function are critical for effective child health practice and policy recommendations. The young brain in particular is highly susceptible to early life experiences, both positive and negative, and thus attention should be paid to the elements that support brain development. Although the young brain is highly plastic and demonstrates potential for recovery from early life insults, the bulk of research evidence suggests that its vulnerability outweighs its plasticity.[5] Thus, support of normal development (eg, through proper nutrition) is far more efficient than trying to restore a neurodevelopmental trajectory after a period of deprivation.

### Developmental Progression of Physical and Anatomic Maturation During Infancy and Early Childhood

The brain is not a homogenous organ. Rather, it is composed of discrete regions (eg, hippocampus, striatum, cortex, cerebellum) and processes (eg, myelination, release and reuptake of neurotransmitters) that have different developmental trajectories. In the article in this supplement titled, "Neurodevelopment, Nutrition, and Inflammation: The Evolving Global Child Health Landscape," Fig 1 demonstrates when these trajectories begin, peak, and end. The vulnerability of any of these regions to a nutrient deficit will depend on the timing of the event, based on the region's requirement for the nutrient at that time. This basic principle exists from conception through the end of brain development, but is particularly accentuated during periods of rapid brain growth and differentiation. One such period is infancy and young childhood.

The postnatal periods of infancy and early childhood are characterized by rapid differentiation of brain regions, such as the visual, auditory, and motor cortices; the limbic system, including the hippocampus; and the cerebellum. These regions mediate fundamental behaviors, such as seeing, hearing, movement, declarative memory, and mixed motor/cognitive functions, respectively. Just as importantly, the integrity of these fundamental structures is key for the construction of connections to later maturing structures (eg, the frontal cortex) that support more complex processing behavior, such as working memory and executive function. Indeed, although the frontal cortex begins to show differentiation as early as infancy, its developmental trajectory is more protracted through young adulthood and thus is vulnerable to nutritional insults both in infancy and later in childhood. Examples

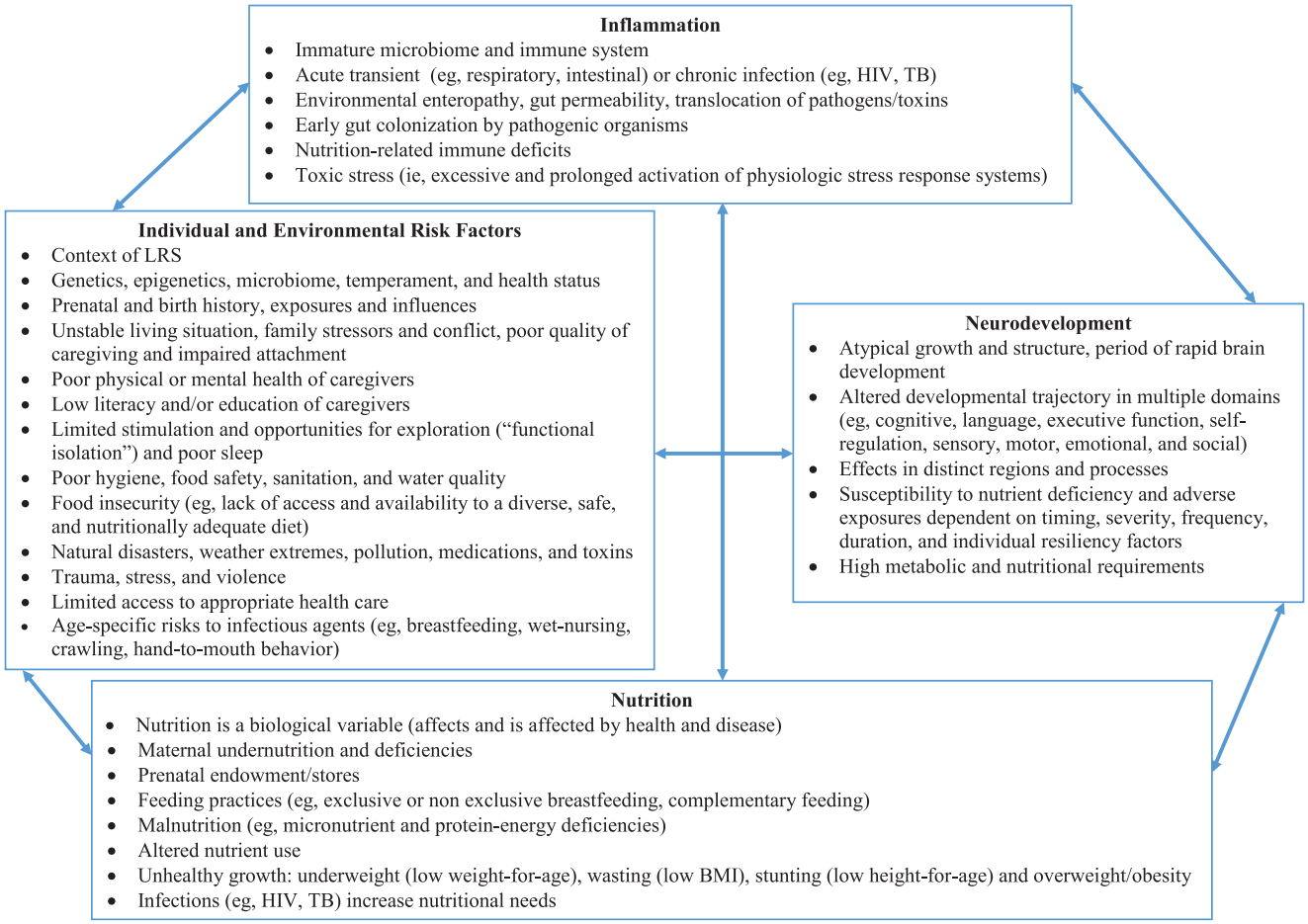


**FIGURE 1**
Relationships among individual and environmental risk factors, inflammation, nutrition, and neurodevelopment for infants in LRS. TB, tuberculosis.

of brainwide processes that are rapidly progressing in infants and toddlers include myelination, which proceeds at a brisk pace from 32 weeks' gestation through 2 to 3 years of age; synaptogenesis, which begins prenatally and continues throughout childhood; and the dopamine neurotransmitter system.

Rapid development of the brain is a highly metabolically taxing process. The young brain accounts for 60% of the body's energy consumption,[6] a figure that contrasts with the adult value of ~20%. Nutrients that support this cellular metabolic rate include glucose, protein (especially branched-chain amino acids), oxygen, iron (for cytochromes), zinc, selenium, and iodine (through regulation of the thyroid). Their integration through signaling cascades, such as the mammalian target of rapamycin system, dictate rates of protein synthesis and actin polymerization in neurons, which in turn are related to dendritic complexity and neuronal functional capacity.[7,8] Thus, deficiencies of these nutrients have more profound negative effects on the brain than other nutrients.

## THE IMPACT OF NUTRITION ON NEURODEVELOPMENT DURING INFANCY

### Human Milk and Breastfeeding (0–6 months)

At the very time when brain development is rapidly progressing, the young infant is uniquely dependent on a single food. Exclusive breastfeeding for young infants is particularly critical for infants in LRS where the risk of exposures to enteric pathogens from contaminated human milk substitutes, fluids and foods is very high. The recommendation in 2001 from the World Health Organization for exclusive breastfeeding for the first 6 months of life[9] emphasized the protective effects against gastrointestinal disease. Importantly, however, the statement acknowledged that the evidence base was insufficient to exclude the potential for micronutrient deficiencies and insufficient intake, especially for infants born with low birth weight and/or to undernourished mothers.

Recent research has raised caution about the robustness of human milk micronutrient composition, particularly for those nutrients in

human milk that are responsive to maternal dietary intake and status: vitamins $B_6$ and $B_{12}$, choline, iodine, and selenium,[10] all of which are directly involved in brain development and function, namely, neurogenesis, differentiation, migration, myelination, and neurotransmitter-related processes.[5] Maternal vitamin $B_{12}$ depletion, whether due to dietary inadequacy or to impaired absorption, has been associated with the development of vitamin $B_{12}$ deficiency in exclusively breastfed infants. Neurologic symptoms of deficiency appeared midway through the first year of life and included cerebral atrophy, loss of developmental milestones, and behavioral and developmental delays. Notably, the deficits were reversible with supplementation in only about half of the cases.[11] Low iodine concentrations in human milk have also been observed in regions with a high prevalence of goiter, and the prevalence of cretinism has been reported in 5% to 15% of breastfed infants in such regions.[12]

For folate, iron, and zinc, 3 micronutrients that are critical to brain development and function,[5] breast milk concentrations are relatively unaffected by maternal intake or status. In the case of iron concentrations, human milk is uniformly low, and the young infant depends primarily on non-dietary factors, such as the use of stores accrued prenatally, delayed cord clamping, and gradual use of iron from the erythron over the early postnatal months. Current estimates of iron requirements of young breastfed infants may not pertain to LMIC, where many infants may be born with a low endowment and yet, in an increasing number of settings, are doubling or tripling in birth weight more rapidly than ever before. In the case of zinc, the concentration in early milk and thus daily transfer to the infant are quite high, are similar across populations, and generally meet the term infant's needs for the first several months of postnatal life. The adequacy of the zinc from human milk alone for low birth weight and premature infants has not been systematically addressed in LRS, but some intervention trials suggest a benefit of zinc supplements.[13] Folate concentrations in human milk, unlike the other B vitamins, are maintained independently of maternal folate status. Infants in both high- and low-resource settings who have been exclusively breastfed for ~6 months have been observed to have normal circulating folate concentrations whether mothers were well-nourished or had marginal nutritional status.[10] The demand for all 3 of these nutrients for the undernourished lactating mother is met by her own tissues, and she may become depleted if her dietary intake is inadequate to support the amounts secreted in milk. In such circumstances, maternal supplementation benefits the mother rather than the infant directly. The impact (direct or indirect) on infant growth and development through improvement in maternal nutritional status during the demanding process of lactation, especially during the early postpartum months, has received relatively little investigation and represents an important research gap.

## Complementary Feeding Period (~6–24 months)

By ~6 months postpartum, exclusive breastfeeding is no longer adequate to meet micronutrient needs, and the quality of complementary foods is critical for the young child's optimal growth and development. This represents another period of great vulnerability. Nearly all of the micronutrients highlighted above as being critical for brain development are found primarily, or in some cases exclusively, in animal-source foods, especially flesh foods. Iodine and long-chain polyunsaturated fatty acids could be considered exceptions. Iodine is often added as a fortificant to salt, rather than consumed within a specific food.[14] Due to both limited availability (eg cost constraints) and to tradition, animal flesh foods are often not offered as complementary foods to young children, and even more infrequently to infants between 6 and 12 months of age.[15,16] Primary reliance on unfortified, plant-based staple foods during the complementary feeding period, even with continued breastfeeding, often results in inadequate intake of several critical micronutrients.[16] Additionally, lower bioavailability of some micronutrients from primarily plant sources (except for some beans) may additionally compromise the adequacy of the intake of a given micronutrient. Undoubtedly, suboptimal complementary feeding quality and quantity contribute to poor linear growth, even though total energy intake may be adequate. The combination, along with the impact of prenatal factors and austere environments associated with poor hygiene and chronic immune stimulation, results in a high prevalence of stunting, with wasting being less common.[17,18] Many of the same factors that contribute to stunting are also likely to impact neurodevelopment during the period of complementary feeding, although trials to specifically isolate and quantify the impact of each factor are lacking.[3]

## Feeding Context and Environment

In addition to the quantity of energy and nutrient intakes, the quality of the feeding process and caregiver responsiveness are also critical for optimal infant and young child development (Fig 1). However, interventions that have investigated the impact of improving the quality of the complementary feeding process specifically on neurodevelopment are limited in LRS. One study in Malawi that employed lipid-based nutrient

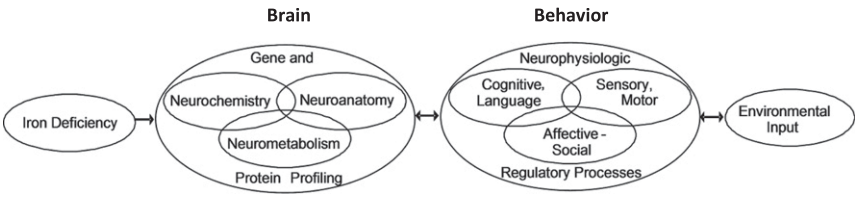


**FIGURE 2**

Iron deficiency and brain development, illustrating connections among iron-dependent changes in brain architecture during development, with examples of altered gene and protein profiles that may regulate these CNS processes. (Reprinted with permission from Lozoff B, Georgieff MK. Iron deficiency and brain development. *Semin Pediatr Neurol.* 2006;13(3):159.)

supplements or a micronutrient-fortified corn–soy flour reported no difference in developmental scores in 18-month-old children after a year-long intervention, but length-for-age *z* score gain and maternal education were both significant predictors of developmental outcomes, supporting the interconnectedness of child development, nutritional intake, growth status, and maternal factors.[19] In a clinical trial studying Indian toddlers, improved complementary feeding alone did not affect development, but guidance around complementary feeding practices in addition to psychosocial stimulation had a significant positive effect on the toddlers' neurodevelopment.[20] These findings support the critical importance of maternal education for fostering enhanced child psychosocial stimulation, improved feeding practices, and improved nutritional status on child development, with or without a substantial impact on linear growth.[21] In addition to the physiologic impact of maternal undernutrition on the mother's health and that of her offspring, nutritional deficiencies have potential adverse effects on maternal cognition and mental status, which in turn exacerbate the risk for low infant stimulation and limited maternal–child responsiveness. Potential interactions between maternal stress and poor nutrition have also recently been reviewed, but the relative contributions of each factor have not yet been elucidated by rigorous field studies.[22]

## Iron as an Example of Nutrient Deficits and Impaired Neurodevelopment

This section concludes with an additional discussion of iron and neurodevelopment, because this micronutrient has the richest evidence base to illustrate several broadly applicable general concepts: powerful interconnections in brain and behavior development; roles of timing, duration, and severity of deficiency; and cooccurrence of nutritional deficiencies with other disadvantages. Iron deficiency is not only the most prevalent micronutrient deficiency in this age group, but its eradication has been challenging and is, as yet, incomplete.

Iron is required for many central nervous system (CNS) processes that are rapidly maturing in infancy and early childhood. Thus, both diffuse and subtle effects would be expected with iron deficiency. The conceptual framework in Fig 2[23] emphasizes the interconnectedness of iron-dependent changes in brain architecture and physiologic "wiring" during development (myelin/dendrites, neurotransmitters, and neurometabolism in specific brain regions) and includes altered gene and protein profiles that may regulate these CNS processes. For behavioral development, changes in sensory, motor, cognitive, language, and socioemotional functioning related to iron deficiency are also interconnected. As noted above and indicated in the Fig 2, brain and behavior effects can be bidirectional, as can environmental influences. Such effects would be expected with other common nutrient deficits in infancy and early childhood, particularly involving those nutrients that affect brain chemistry, anatomy, and metabolism.[5]

Initial studies linking fetal and neonatal iron deficiency involved neonates with other risk factors for compromised development, such as prematurity, maternal diabetes, or intrauterine growth restriction.[24] The handful of studies involving term infants of uncomplicated pregnancies suggest short- and long-term effects.[25–29] The different neurodevelopmental impacts of fetal–neonatal versus postnatal iron deficiency in humans are unknown, but the time course of brain development suggests there would be differential effects. That is, outcomes would be worse when a nutrient deficiency starts earlier, lasts longer, or is more severe. The sole study of adult outcomes involved iron deficiency that was probably chronic during infancy, because iron deficiency anemia was detected (and treated) at 12 to 23 months of age in a sample of infants in Costa Rica. There were poorer functional outcomes at 25 years of age, despite correction of iron deficiency anemia in infancy. Specifically, previously iron-deficient individuals were less likely to complete secondary school, to have pursued additional training, or to have married.[30]

Human studies have also turned to randomized controlled trials (RCTs) of prophylactic iron supplementation (rather than treatment) to strengthen causal inferences. The effects on neurodevelopment are less consistent or pronounced in such trials versus in studies that compare neurodevelopment in infants with or without iron deficiency. In fact, some meta-analyses conclude that there are no effects of iron supplementation,[31,32] in contrast

**TABLE 1** Recommendations for Research Initiatives To Address Knowledge Gaps

| Problem or Question | Studies Needed |
|---|---|
| 1. Gaps in knowledge related to nutrition and neurodevelopment/brain function during infancy | |
| What are the critical interactions of nutrient deficiencies and inflammation/infection on brain development and neurodevelopment? What is the impact of timing of such insults on outcomes? | Testing in animal models brain and behavioral effects of nutrient deficiencies, inflammation/infection, and their interactions. |
| How can micronutrients critical to the developing brain reach the relevant brain regions more effectively? | Investigations of novel micronutrient delivery systems on neural systems. |
| To what extent does maternal malnutrition impact human milk composition and infant brain development? | Characterize the maternal sensitive micronutrient profile in human milk in vulnerable populations.<br>Conduct interventions in pregnant and lactating women to mitigate the risk of human milk –transmitted deficiencies in young infants in vulnerable settings. |
| 2. Gaps in knowledge related to inflammation, infection, and neurodevelopment/brain function during infancy | |
| Need to better understand the roles and interaction of the microbiome, micronutrient availability, inflammation, and neurodevelopment. | Develop strategies to mitigate gut inflammation and dysbiosis.<br>Identify microbiota profiles associated with improved micronutrient bioavailability and functional neurodevelopmental outcomes. |
| 3. Gaps in knowledge related to interactions of nutrition, inflammation, neurodevelopment, and other influencing factors during infancy | |
| Current assessment tools are not sufficiently sensitive to detect subtle deficits in neurodevelopment in infants and young children. | Develop field-friendly, brain-based measures that can, especially in LRS, meaningfully assess multiple domains in the infant and young child and yield predictive value for later function and benefit of early intervention. |
| What is the functional significance of diffuse but mild deficits in neurodevelopment? | Conduct long-term follow-up studies to refine prognostic understanding of early deficits. |
| What is the balance between environmental exposures and genetic vulnerability and protection against micronutrient deficiencies? | Investigate effects of potentially toxic environmental exposures and their interactions with micronutrient deficiencies on neurodevelopment. |
| 4. Gaps in knowledge related to evidence-based interventions for optimal neurodevelopmental outcomes during infancy | |
| Multiple insults are likely to adversely impact neurodevelopment. | Conduct studies designed and powered to assess for multiple insults (eg, micronutrient deficiency, neurotoxins, stress, inflammation).<br>Develop "bundled" interventions to evaluate impact on global neurodevelopment. |
| What are the epigenetic effects of interventions? | Incorporate evaluation of epigenetic modifications (eg, methylation) in intervention studies in mothers, infants, and young children. |

to several studies showing poorer outcomes in iron-deficient infants.[24,33–36] Additional considerations help us understand this apparent paradox. RCTs in populations where iron deficiency is uncommon may require huge sample sizes to detect statistically and clinically meaningful effects. RCTs in populations where iron deficiency is widespread may not provide sufficient iron if prophylactic doses are used, and supplementation may begin after neurodevelopment has already been compromised by lack of iron for many infants. Consequently, improved analytic methods and study designs are needed to investigate these intersecting scientific areas.

Few studies to date have considered the impact of maternal iron supplementation on fetal–neonatal iron status. A recent RCT in China showed marked improvements in maternal iron status with supplemental iron, but many women were still iron deficient at or near term, and there was no effect on cord blood measures of fetal–neonatal iron status.[37] In this same trial, iron supplementation during infancy was associated with significantly improved motor scores compared with placebo or with supplementation during pregnancy alone.[38]

## THE IMPACT OF INFLAMMATION ON NEURODEVELOPMENT DURING INFANCY

The evidence base for the direct impact of inflammation, resulting from both infectious and noninfectious causes, on neurodevelopment is even more limited than that for nutrient use. The recent outbreak of Zika virus infection has drawn attention to the striking effects of infection occurring early in gestation, notably manifest as severe microcephaly. In a prospective study, 29% of women found to have become infected at various time points throughout pregnancy had adverse effects that extended beyond the most severe brain insults to also include placental insufficiency, intrauterine growth restriction, and milder central nervous system injury.[39] Thus, the full extent of infection during gestation on offspring neurodevelopmental outcomes is unknown, but early findings suggest that this may represent an important additional burden

for LRS. The acute and long-term consequences of new Zika virus infection in infancy are unknown, but pose a theoretical risk for neurodevelopmental sequelae.

The connection between stunting, which is mediated in part by chronic inflammation, and impaired child development has clearly been documented, particularly in older children. Such associations include less exploratory behavior, poorer cognitive achievement, more anxiety, and lower school performance.[18] A recent large prospective observational study in Bangladesh directly assessed the association of biomarkers of inflammation at 6 months of age on motor and cognitive function at 12 and 24 months of age. In this cohort, fever and inflammation were strongly associated with significantly lower scores on language, cognitive, and motor tests.[40] In the same cohort, high rates of anemia and zinc deficiency were also observed, with rates being highest in the first year of life when processes of brain maturation are particularly active.[41] New insights regarding the links between inflammation and neurodevelopment will undoubtedly emerge in coming years, as prospective data linking growth, feeding, and nutrient-intake patterns, gut function and the microbiota, inflammation, and developmental testing from other high-risk populations become available.[41,42]

## THE INTERACTION OF NUTRITION, INFLAMMATION, NEURODEVELOPMENT, AND OTHER INFLUENCING FACTORS DURING INFANCY

The pervasive and substantial exposures to environments with contaminated water and to poor hygiene are increasingly recognized to contribute to the early postnatal linear growth faltering and stunting observed in LMIC.[43] Although stunting is undoubtedly multifactorial and includes chronic malnutrition, environmental enteric dysfunction, a chronic inflammatory condition of the intestinal tract that starts in early infancy,[44,45] is increasingly recognized to impact nutrient use, growth, and neurodevelopment. For example, the central role of hepcidin in the regulation of iron homeostasis powerfully illustrates a biological balance between the need for adequate intake of an essential nutrient and the countering effect of immune stimulation to inhibit iron absorption and use. Although a similar "master regulator" analogous to hepcidin has not been identified for other micronutrients, data are emerging to suggest adverse effects of environmental enteric dysfunction and inflammation on zinc absorption and homeostasis.[13,46,47] Another mechanism by which disrupted gut health may impact development is through alterations in the gut microbiota which, through interaction with the developing innate immune system, can drive elevations in proinflammatory and antiinflammatory cytokines and influence brain function.[48] Such early and enduring inflammatory stimuli have also been linked to a risk of systemic metabolic disease associated with later noncommunicable diseases, particularly in settings where access to more abundant caloric intake is emerging. In recent years, this constellation has been termed the "stunting syndrome,"[18] reflecting the multifactorial and self-perpetuating nature of the condition. Such recognition now underpins consideration of effective interventions that encompass approaches well beyond nutrient intakes alone and that attempt to mitigate other negative environmental factors and host exposures.[4,49]

## IMPLICATIONS FOR RESEARCH, PROGRAM, AND POLICY DEVELOPMENT

The period from birth through 24 months of age represents a strongly compelling illustration of the interactions among maternal and infant nutritional status, environmental exposures, inflammation, and the rapidly developing brain. A list of knowledge gaps and research priorities is provided in Table 1. Although this complexity mandates multisectoral interventions to maximize benefits, the evidence base is more than adequate to prioritize selected nutrition-specific and nutrition-sensitive elements, especially in the most socioeconomically deprived settings.[21,49] Despite the numerous vulnerabilities for infants and young children highlighted in this paper, highest yields for improved neurodevelopment seem likely to be realized by bundled interventions that focus on improved maternal nutritional status through the entire reproductive cycle, including lactation; promoting and supporting exclusive breastfeeding for nutritional benefits and for limiting infant contaminant exposures; enhancing the quality of complementary foods as well as the feeding process; enabling maternal education to improve parenting and infant stimulation (among numerous other benefits); and improving hygiene and sanitation to reduce the drivers of high-inflammatory burdens. As multidimensional programs aiming to broadly improve infant and young child feeding are developed, rigorous process evaluation should be a cornerstone to enable identification of the key effective components. Examples of program impact evaluation have recently been published.[50,51] Thus, beyond traditional research trials to examine biological outcomes, such dissemination and implementation studies are critical to move from identification of best practices to best programs and policies. With

progress in each of these domains, the potential benefits in human capital would be realized for both individuals and populations in both short- and long-term time frames.

**ABBREVIATIONS**

CNS: central nervous system
LMIC: low- and middle-income countries
LRS: low-resource setting
RCT: randomized controlled trial

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Estimates of the burden of neurodevelopmental impairments in low- and middle-income countries (LMIC) are limited and highly variable, but are generally reported to be higher than in high-resource settings. In all settings, the prevalence of mild impairments is higher than severe disability.[1,2] Among several factors identified as contributors to developmental disabilities in LMIC, infections and malnutrition, including micronutrient deficiencies, are particularly important and potentially modifiable.[3]

Infancy and early childhood (ie, birth through age 24 months) represent a period of life with both exquisite opportunity and vulnerability for neurodevelopment. Not only are many aspects of brain development undergoing rapid anatomic and functional expansion during this postnatal component of the "1000 days critical window," but nutrient requirements are also high due to rapid physical growth and maturation. The complex interactions that exist among nutritional status (deficits and surfeits) as well as the social and physical environments and exposures they entail are particularly potent during this period of rapid change. Furthermore, the interactions are bidirectional, such that the developing infant not only responds to his/her environment but also, in ideal circumstances, elicits responses from adult care providers that additionally stimulate more inputs. The newborn brain also reflects maternal exposures that occurred as the product of many interacting forces during gestation.

The connections between nutrient use (absorption, excretion, and retention) and acute and chronic inflammation and stress are increasingly recognized.[4] Recent reviews have addressed selected aspects of this sensitive period, but the evidence base linking both nutrition and inflammation to neurodevelopment is only modest and even more limited for this young age group specifically. This article in the supplement will provide an overview of key aspects of interactions that are

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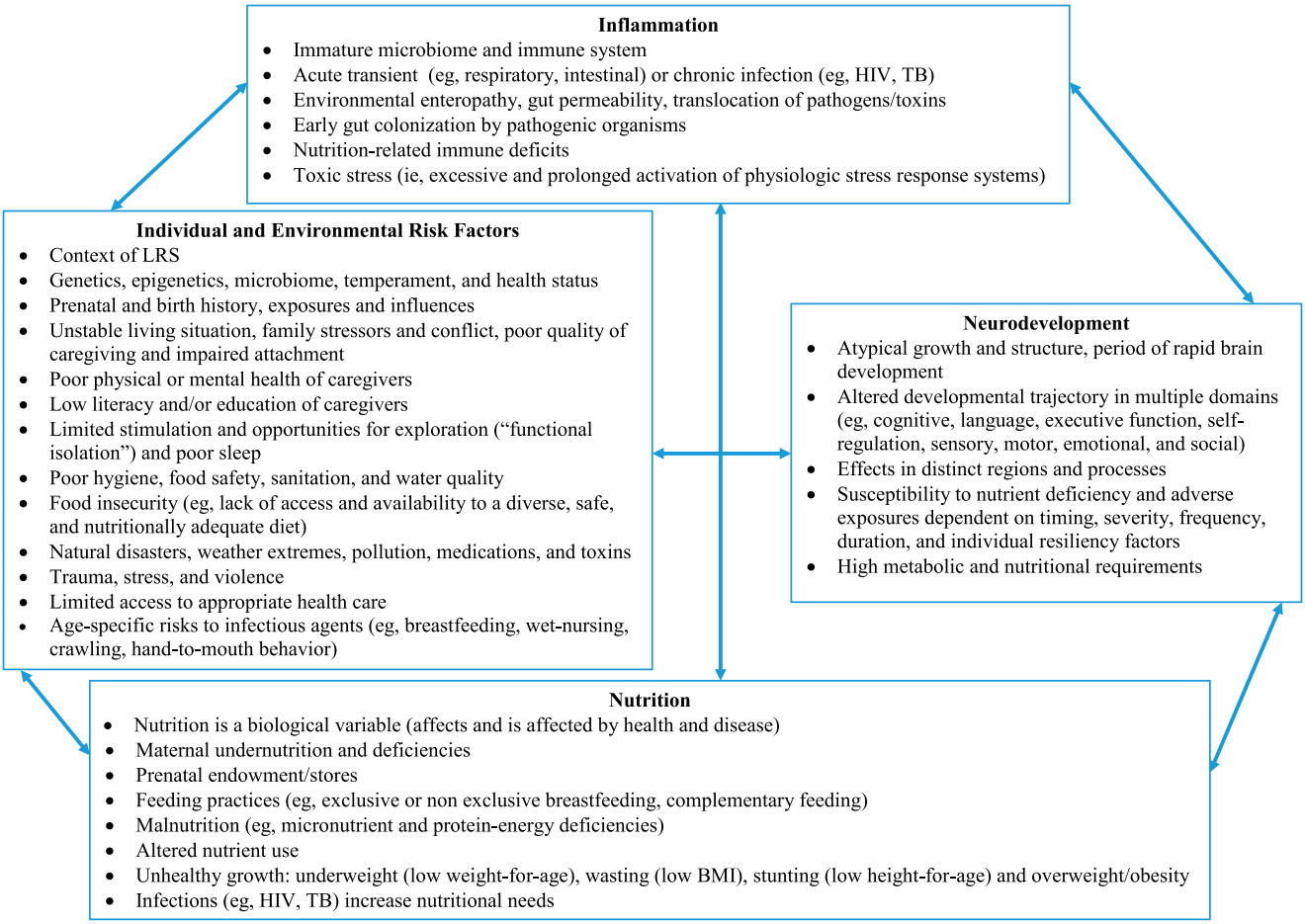


**FIGURE 1**
Relationships among individual and environmental risk factors, inflammation, nutrition, and neurodevelopment for infants in LRS. TB, tuberculosis.

particularly relevant to the infant and young child during this critical developmental stage. The underlying framework reflecting these interrelationships and the issues particular to infants in low-resource settings (LRS) are depicted in Fig 1. Furthermore, emphasis will be placed on these sectors as they exist in, and are impacted by, environments in LRS. To advance the field, knowledge gaps and research priorities will be highlighted.

## KEY NEURODEVELOPMENTAL CONSIDERATIONS DURING INFANCY

The concept of neurodevelopment for the infant and young child includes multiple behavioral domains: motor, mental, sensory, and socioemotional. It is important to understand that these behaviors are the expression of the brain's activity. Thus, understanding brain development and the roles that nutrients and inflammation play in shaping its development and function are critical for effective child health practice and policy recommendations. The young brain in particular is highly susceptible to early life experiences, both positive and negative, and thus attention should be paid to the elements that support brain development. Although the young brain is highly plastic and demonstrates potential for recovery from early life insults, the bulk of research evidence suggests that its vulnerability outweighs its plasticity.[5] Thus, support of normal development (eg, through proper nutrition) is far more efficient than trying to restore a neurodevelopmental trajectory after a period of deprivation.

### Developmental Progression of Physical and Anatomic Maturation During Infancy and Early Childhood

The brain is not a homogenous organ. Rather, it is composed of discrete regions (eg, hippocampus, striatum, cortex, cerebellum) and processes (eg, myelination, release, and reuptake of neurotransmitters) that have different developmental trajectories. In the article in this supplement titled, "Neurodevelopment, Nutrition, and Inflammation: The Evolving Global Child Health Landscape, " Fig 1 demonstrates when these trajectories begin, peak, and end. The

vulnerability of any of these regions to a nutrient deficit will depend on the timing of the event, based on the region's requirement for the nutrient at that time. This basic principle exists from conception through the end of brain development, but is particularly accentuated during periods of rapid brain growth and differentiation. One such period is infancy and young childhood.

The postnatal periods of infancy and early childhood are characterized by rapid differentiation of brain regions, such as the visual, auditory, and motor cortices; the limbic system, including the hippocampus; and the cerebellum. These regions mediate fundamental behaviors, such as seeing, hearing, movement, declarative memory, and mixed motor/cognitive functions, respectively. Just as importantly, the integrity of these fundamental structures is key for the construction of connections to later maturing structures (eg, the frontal cortex) that support more complex processing behavior, such as working memory and executive function. Indeed, although the frontal cortex begins to show differentiation as early as infancy, its developmental trajectory is more protracted through young adulthood and thus is vulnerable to nutritional insults both in infancy and later in childhood. Examples of brainwide processes that are rapidly progressing in infants and toddlers include myelination, which proceeds at a brisk pace from 32 weeks' gestation through 2 to 3 years of age; synaptogenesis, which begins prenatally and continues throughout childhood; and the dopamine neurotransmitter system.

Rapid development of the brain is a highly metabolically taxing process. The young brain accounts for 60% of the body's energy consumption, [6] a figure that contrasts with the adult value of ~20%. Nutrients that support this cellular metabolic rate include glucose, protein (especially branched-chain amino acids), oxygen, iron (for cytochromes), zinc, selenium, and iodine (through regulation of the thyroid). Their integration through signaling cascades, such as the mammalian target of rapamycin system, dictate rates of protein synthesis and actin polymerization in neurons, which in turn are related to dendritic complexity and neuronal functional capacity.[7,8] Thus, deficiencies of these nutrients have more profound negative effects on the brain than other nutrients.

## THE IMPACT OF NUTRITION ON NEURODEVELOPMENT DURING INFANCY

### Human Milk and Breastfeeding (0–6 months)

At the very time when brain development is rapidly progressing, the young infant is uniquely dependent on a single food. Exclusive breastfeeding for young infants is particularly critical for infants in LRS where the risk of exposures to enteric pathogens from contaminated human milk substitutes, fluids and foods is very high. The recommendation in 2001 from the World Health Organization for exclusive breastfeeding for the first 6 months of life[9] emphasized the protective effects against gastrointestinal disease. Importantly, however, the statement acknowledged that the evidence base was insufficient to exclude the potential for micronutrient deficiencies and insufficient intake, especially for infants born with low birth weight and/or to undernourished mothers.

Recent research has raised caution about the robustness of human milk micronutrient composition, particularly for those nutrients in human milk that are responsive to maternal dietary intake and status: vitamins $B_6$ and $B_{12}$, choline, iodine, and selenium,[10] all of which are directly involved in brain development and function, namely, neurogenesis, differentiation, migration, myelination, and neurotransmitter-related processes.[5] Maternal vitamin $B_{12}$ depletion, whether due to dietary inadequacy or to impaired absorption, has been associated with the development of vitamin $B_{12}$ deficiency in exclusively breastfed infants. Neurologic symptoms of deficiency appeared midway through the first year of life and included cerebral atrophy, loss of developmental milestones, and behavioral and developmental delays. Notably, the deficits were reversible with supplementation in only about half of the cases.[11] Low iodine concentrations in human milk have also been observed in regions with a high prevalence of goiter, and the prevalence of cretinism has been reported in 5% to 15% of breastfed infants in such regions.[12]

For folate, iron, and zinc, 3 micronutrients that are critical to brain development and function, [5] breast milk concentrations are relatively unaffected by maternal intake or status. In the case of iron concentrations, human milk is uniformly low, and the young infant depends primarily on non-dietary factors, such as the use of stores accrued prenatally, delayed cord clamping, and gradual use of iron from the erythron over the early postnatal months. Current estimates of iron requirements of young breastfed infants may not pertain to LMIC, where many infants may be born with a low endowment and yet, in an increasing number of settings, are doubling or tripling in birth weight more rapidly than ever before. In the case of zinc, the concentration in early milk and thus daily transfer to the infant are quite high, are similar across populations, and generally meet the term infant's needs for the first several months of postnatal life. The adequacy of the zinc from human milk alone for low birth weight and

premature infants has not been systematically addressed in LRS, but some intervention trials suggest a benefit of zinc supplements.[13] Folate concentrations in human milk, unlike the other B vitamins, are maintained independently of maternal folate status. Infants in both high- and low-resource settings who have been exclusively breastfed for ~6 months have been observed to have normal circulating folate concentrations whether mothers were well-nourished or had marginal nutritional status.[10] The demand for all 3 of these nutrients for the undernourished lactating mother is met by her own tissues, and she may become depleted if her dietary intake is inadequate to support the amounts secreted in milk. In such circumstances, maternal supplementation benefits the mother rather than the infant directly. The impact (direct or indirect) on infant growth and development through improvement in maternal nutritional status during the demanding process of lactation, especially during the early postpartum months, has received relatively little investigation and represents an important research gap.

## Complementary Feeding Period (~6–24 months)

By ~6 months postpartum, exclusive breastfeeding is no longer adequate to meet micronutrient needs, and the quality of complementary foods is critical for the young child's optimal growth and development. This represents another period of great vulnerability. Nearly all of the micronutrients highlighted above as being critical for brain development are found primarily, or in some cases exclusively, in animal-source foods, especially flesh foods. Iodine and long-chain polyunsaturated fatty acids could be considered exceptions. Iodine is often added as a fortificant to salt, rather than consumed within a specific food.[14] Due to both limited availability (eg cost constraints) and to tradition, animal flesh foods are often not offered as complementary foods to young children, and even more infrequently to infants between 6 and 12 months of age.[15,16] Primary reliance on unfortified, plant-based staple foods during the complementary feeding period, even with continued breastfeeding, often results in inadequate intake of several critical micronutrients.[16] Additionally, lower bioavailability of some micronutrients from primarily plant sources (except for some beans) may additionally compromise the adequacy of the intake of a given micronutrient. Undoubtedly, suboptimal complementary feeding quality and quantity contribute to poor linear growth, even though total energy intake may be adequate. The combination, along with the impact of prenatal factors and austere environments associated with poor hygiene and chronic immune stimulation, results in a high prevalence of stunting, with wasting being less common.[17,18] Many of the same factors that contribute to stunting are also likely to impact neurodevelopment during the period of complementary feeding, although trials to specifically isolate and quantify the impact of each factor are lacking.[3]

## Feeding Context and Environment

In addition to the quantity of energy and nutrient intakes, the quality of the feeding process and caregiver responsiveness are also critical for optimal infant and young child development (Fig 1). However, interventions that have investigated the impact of improving the quality of the complementary feeding process specifically on neurodevelopment are limited in LRS. One study in Malawi that employed lipid-based nutrient supplements or a micronutrient-fortified corn–soy flour reported no difference in developmental scores in 18-month-old children after a year-long intervention, but length-for-age *z* score gain and maternal education were both significant predictors of developmental outcomes, supporting the interconnectedness of child development, nutritional intake, growth status, and maternal factors.[19] In a clinical trial studying Indian toddlers, improved complementary feeding alone did not affect development, but guidance around complementary feeding practices in addition to psychosocial stimulation had a significant positive effect on the toddlers' neurodevelopment.[20] These findings support the critical importance of maternal education for fostering enhanced child psychosocial stimulation, improved feeding practices, and improved nutritional status on child development, with or without a substantial impact on linear growth.[21] In addition to the physiologic impact of maternal undernutrition on the mother's health and that of her offspring, nutritional deficiencies have potential adverse effects on maternal cognition and mental status, which in turn exacerbate the risk for low infant stimulation and limited maternal–child responsiveness. Potential interactions between maternal stress and poor nutrition have also recently been reviewed, but the relative contributions of each factor have not yet been elucidated by rigorous field studies.[22]

## Iron as an Example of Nutrient Deficits and Impaired Neurodevelopment

This section concludes with an additional discussion of iron and neurodevelopment, because this micronutrient has the richest evidence base to illustrate several broadly applicable general concepts: powerful interconnections in brain and behavior development; roles of timing, duration, and severity of deficiency; and cooccurrence of nutritional deficiencies with other disadvantages. Iron deficiency

is not only the most prevalent micronutrient deficiency in this age group, but its eradication has been challenging and is, as yet, incomplete.

Iron is required for many central nervous system (CNS) processes that are rapidly maturing in infancy and early childhood. Thus, both diffuse and subtle effects would be expected with iron deficiency. The conceptual framework in Fig 2[23] emphasizes the interconnectedness of iron-dependent changes in brain architecture and physiologic "wiring" during development (myelin/dendrites, neurotransmitters, and neurometabolism in specific brain regions) and includes altered gene and protein profiles that may regulate these CNS processes. For behavioral development, changes in sensory, motor, cognitive, language, and socioemotional functioning related to iron deficiency are also interconnected. As noted above and indicated in the Fig 2, brain and behavior effects can be bidirectional, as can environmental influences. Such effects would be expected with other common nutrient deficits in infancy and early childhood, particularly involving those nutrients that affect brain chemistry, anatomy, and metabolism.[5]

Initial studies linking fetal and neonatal iron deficiency involved neonates with other risk factors for compromised development, such as prematurity, maternal diabetes, or intrauterine growth restriction.[24] The handful of studies involving term infants of uncomplicated pregnancies suggest short- and long-term effects.[25–29] The different neurodevelopmental impacts of fetal–neonatal versus postnatal iron deficiency in humans are unknown, but the time course of brain development suggests there would be differential effects. That is, outcomes would be worse when a nutrient deficiency starts earlier, lasts longer, or is more severe. The

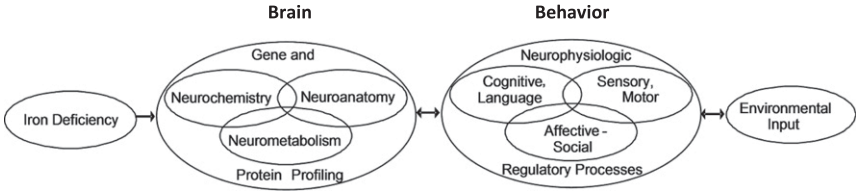


**FIGURE 2**

Iron deficiency and brain development, illustrating connections among iron-dependent changes in brain architecture during development, with examples of altered gene and protein profiles that may regulate these CNS processes. (Reprinted with permission from Lozoff B, Georgieff MK. Iron deficiency and brain development. *Semin Pediatr Neurol.* 2006;13(3):159.)

sole study of adult outcomes involved iron deficiency that was probably chronic during infancy, because iron deficiency anemia was detected (and treated) at 12 to 23 months of age in a sample of infants in Costa Rica. There were poorer functional outcomes at 25 years of age, despite correction of iron deficiency anemia in infancy. Specifically, previously iron-deficient individuals were less likely to complete secondary school, to have pursued additional training, or to have married.[30]

Human studies have also turned to randomized controlled trials (RCTs) of prophylactic iron supplementation (rather than treatment) to strengthen causal inferences. The effects on neurodevelopment are less consistent or pronounced in such trials versus in studies that compare neurodevelopment in infants with or without iron deficiency. In fact, some meta-analyses conclude that there are no effects of iron supplementation,[31,32] in contrast to several studies showing poorer outcomes in iron-deficient infants.[24,33–36] Additional considerations help us understand this apparent paradox. RCTs in populations where iron deficiency is uncommon may require huge sample sizes to detect statistically and clinically meaningful effects. RCTs in populations where iron deficiency is widespread may not provide sufficient iron if prophylactic doses are used, and supplementation may begin after neurodevelopment has already been compromised by lack of iron for many infants. Consequently, improved analytic methods and study designs are needed to investigate these intersecting scientific areas.

Few studies to date have considered the impact of maternal iron supplementation on fetal–neonatal iron status. A recent RCT in China showed marked improvements in maternal iron status with supplemental iron, but many women were still iron deficient at or near term, and there was no effect on cord blood measures of fetal–neonatal iron status.[37] In this same trial, iron supplementation during infancy was associated with significantly improved motor scores compared with placebo or with supplementation during pregnancy alone.[38]

## THE IMPACT OF INFLAMMATION ON NEURODEVELOPMENT DURING INFANCY

The evidence base for the direct impact of inflammation, resulting from both infectious and noninfectious causes, on neurodevelopment is even more limited than that for nutrient use. The recent outbreak of Zika virus infection has drawn attention to the striking effects of infection occurring early in gestation, notably manifest as severe microcephaly. In a prospective study, 29% of women found to have become infected at various time points throughout pregnancy had adverse effects that extended beyond the most severe brain insults to also include

placental insufficiency, intrauterine growth restriction, and milder central nervous system injury.[39] Thus, the full extent of infection during gestation on offspring neurodevelopmental outcomes is unknown, but early findings suggest that this may represent an important additional burden for LRS. The acute and long-term consequences of new Zika virus infection in infancy are unknown, but pose a theoretical risk for neurodevelopmental sequelae.

The connection between stunting, which is mediated in part by chronic inflammation, and impaired child development has clearly been documented, particularly in older children. Such associations include less exploratory behavior, poorer cognitive achievement, more anxiety, and lower school performance.[18] A recent large prospective observational study in Bangladesh directly assessed the association of biomarkers of inflammation at 6 months of age on motor and cognitive function at 12 and 24 months of age. In this cohort, fever and inflammation were strongly associated with significantly lower scores on language, cognitive, and motor tests.[40] In the same cohort, high rates of anemia and zinc deficiency were also observed, with rates being highest in the first year of life when processes of brain maturation are particularly active.[41] New insights regarding the links between inflammation and neurodevelopment will undoubtedly emerge in coming years, as prospective data linking growth, feeding, and nutrient-intake patterns, gut function and the microbiota, inflammation, and developmental testing from other high-risk populations become available.[41,42]

## THE INTERACTION OF NUTRITION, INFLAMMATION, NEURODEVELOPMENT, AND OTHER INFLUENCING FACTORS DURING INFANCY

The pervasive and substantial exposures to environments with contaminated water and to poor hygiene are increasingly recognized to contribute to the early postnatal linear growth faltering and stunting observed in LMIC.[43] Although stunting is undoubtedly multifactorial and includes chronic malnutrition, environmental enteric dysfunction, a chronic inflammatory condition of the intestinal tract that starts in early infancy,[44,45] is increasingly recognized to impact nutrient use, growth, and neurodevelopment. For example, the central role of hepcidin in the regulation of iron homeostasis powerfully illustrates a biological balance between the need for adequate intake of an essential nutrient and the countering effect of immune stimulation to inhibit iron absorption and use. Although a similar "master regulator" analogous to hepcidin has not been identified for other micronutrients, data are emerging to suggest adverse effects of environmental enteric dysfunction and inflammation on zinc absorption and homeostasis.[13,46,47] Another mechanism by which disrupted gut health may impact development is through alterations in the gut microbiota which, through interaction with the developing innate immune system, can drive elevations in proinflammatory and antiinflammatory cytokines and influence brain function.[48] Such early and enduring inflammatory stimuli have also been linked to a risk of systemic metabolic disease associated with later noncommunicable diseases, particularly in settings where access to more abundant caloric intake is emerging. In recent years, this constellation has been termed the "stunting syndrome," [18] reflecting the multifactorial and self-perpetuating nature of the condition. Such recognition now underpins consideration of effective interventions that encompass approaches well beyond nutrient intakes alone and that attempt to mitigate other negative environmental factors and host exposures.[4,49]

## IMPLICATIONS FOR RESEARCH, PROGRAM, AND POLICY DEVELOPMENT

The period from birth through 24 months of age represents a strongly compelling illustration of the interactions among maternal and infant nutritional status, environmental exposures, inflammation, and the rapidly developing brain. A list of knowledge gaps and research priorities is provided in Table 1. Although this complexity mandates multisectoral interventions to maximize benefits, the evidence base is more than adequate to prioritize selected nutrition-specific and nutrition-sensitive elements, especially in the most socioeconomically deprived settings.[21,49] Despite the numerous vulnerabilities for infants and young children highlighted in this paper, highest yields for improved neurodevelopment seem likely to be realized by bundled interventions that focus on improved maternal nutritional status through the entire reproductive cycle, including lactation; promoting and supporting exclusive breastfeeding for nutritional benefits and for limiting infant contaminant exposures; enhancing the quality of complementary foods as well as the feeding process; enabling maternal education to improve parenting and infant stimulation (among numerous other benefits); and improving hygiene and sanitation to reduce the drivers of high-inflammatory burdens. As multidimensional programs aiming to broadly improve infant and young child feeding

**TABLE 1** Recommendations for Research Initiatives To Address Knowledge Gaps

| Problem or Question | Studies Needed |
|---|---|
| 1. Gaps in knowledge related to nutrition and neurodevelopment/brain function during infancy | |
| What are the critical interactions of nutrient deficiencies and inflammation/infection on brain development and neurodevelopment? What is the impact of timing of such insults on outcomes? | Testing in animal models brain and behavioral effects of nutrient deficiencies, inflammation/infection, and their interactions. |
| How can micronutrients critical to the developing brain reach the relevant brain regions more effectively? | Investigations of novel micronutrient delivery systems on neural systems. |
| To what extent does maternal malnutrition impact human milk composition and infant brain development? | Characterize the maternal sensitive micronutrient profile in human milk in vulnerable populations.<br>Conduct interventions in pregnant and lactating women to mitigate the risk of human milk –ransmitted deficiencies in young infants in vulnerable settings. |
| 2. Gaps in knowledge related to inflammation, infection, and neurodevelopment/brain function during infancy | |
| Need to better understand the roles and interaction of the microbiome, micronutrient availability, inflammation, and neurodevelopment. | Develop strategies to mitigate gut inflammation and dysbiosis.<br>Identify microbiota profiles associated with improved micronutrient bioavailability and functional neurodevelopmental outcomes. |
| 3. Gaps in knowledge related to interactions of nutrition, inflammation, neurodevelopment, and other influencing factors during infancy | |
| Current assessment tools are not sufficiently sensitive to detect subtle deficits in neurodevelopment in infants and young children. | Develop field-friendly, brain-based measures that can, especially in resource limited settings:<br>meaningfully assess multiple domains in the infant and young child;<br>yield predictive value for later function and benefit of early intervention |
| What is the functional significance of diffuse but mild deficits in neurodevelopment? | Conduct long-term follow-up studies to refine prognostic understanding of early deficits. |
| What is the balance between environmental exposures and genetic vulnerability and protection against micronutrient deficiencies? | Investigate effects of potentially toxic environmental exposures and their interactions with micronutrient deficiencies on neurodevelopment. |
| 4. Gaps in knowledge related to evidence-based interventions for optimal neurodevelopmental outcomes during infancy | |
| Multiple insults are likely to adversely impact neurodevelopment. | Conduct studies designed and powered to assess for multiple insults (eg, micronutrient deficiency, neurotoxins, stress, inflammation).<br>Develop "bundled" interventions to evaluate impact on global neurodevelopment. |
| What are the epigenetic effects of interventions? | Incorporate evaluation of epigenetic modifications (eg, methylation) in intervention studies in mothers, infants, and young children. |

are developed, rigorous process evaluation should be a cornerstone to enable identification of the key effective components. Examples of program impact evaluation have recently been published.[50,51] Thus, beyond traditional research trials to examine biological outcomes, such dissemination and implementation studies are critical to move from identification of best practices to best programs and policies. With progress in each of these domains, the potential benefits in human capital would be realized for both individuals and populations in both short- and long-term time frames.

**ABBREVIATIONS**

CNS: central nervous system
LMIC: low- and middle-income countries
LRS: low-resource setting
RCT: randomized controlled trial

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