Neurodevelopment, Nutrition, and Inflammation: The Evolving Global Child Health Landscape

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Dr Bhutta was a presenter at the original Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) scientific meeting, served as the lead author for the paper, organized the writing team, drafted the initial manuscript, incorporated edits from the additional authors and editors, and finalized the manuscript; Dr Guerrant was a presenter at the original NICHD scientific meeting, contributed to the writing of the initial manuscript, and reviewed and revised subsequent versions of the manuscript; Dr Nelson was a panelist at the original NICHD scientific meeting, contributed to the writing of the initial manuscript, and reviewed and revised subsequent versions of the manuscript; and all authors approved the final manuscript as submitted and are accountable for all aspects of the work.

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The last decade has witnessed major reductions in child mortality and a focus on saving lives with key interventions targeting major causes of child deaths, such as neonatal deaths and those due to childhood diarrhea and pneumonia. With the transition to Sustainable Development Goals, the global health community is expanding child health initiatives to address not only the ongoing need for reduced mortality, but also to decrease morbidity and adverse exposures toward improving health and developmental outcomes. The relationship between adverse environmental exposures frequently associated with factors operating in the prepregnancy period and during fetal development is well established. Also well appreciated are the developmental impacts (both short- and long-term) associated with postnatal factors, such as immunostimulation and environmental enteropathy, and the additional risks posed by the confluence of factors related to malnutrition, poor living conditions, and the high burden of infections. This article provides our current thinking on the pathogenesis and risk factors for adverse developmental outcomes among young children, setting the scene for potential interventions that can ameliorate these adversities among families and children at risk.

abstract

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Important and heartening downward trends in global mortality for children <5 years of age have been achieved in recent years. For a summary, see Table 1. In light of this encouraging progress, there is an emerging recognition of the importance of newborn survival in reducing child mortality. Strategies to address newborn survival will also be a critical part of the maternal and child health goals within the United Nations’ Sustainable Development Goal 3 for health and well-being. Although global burden of disease data have typically focused on children <5 years of age, more recent evidence points to a continued burden of morbidity and ill health among older children and adolescents.

Increasingly, the global health community is expanding child health initiatives to address not only the ongoing need for reduced mortality, but also to decrease morbidity and adverse exposures toward improving health and developmental outcomes. In addition, reductions in child mortality have not been universally realized and significant disparities exist for marginalized populations. According to the 2016 Global Nutrition Report, 159 million children have stunted growth worldwide, reflecting a rate of reduction that is far lower than the targets set by the World Health Assembly. The data suggest that, notwithstanding the leading infectious disease–associated deaths, iron deficiency anemia was the leading cause of years lived with disability among children and adolescents, affecting 619 million children in 2013. Not only are developmental deficits important consequences of conditions associated with a higher risk of mortality (such as intraterine growth restriction, prematurity, and birth asphyxia), but they may also be associated with a range of factors related to living conditions (eg, sanitation), poverty, and undernutrition. More recently, the association of Zika virus infection during pregnancy and microcephaly highlights the importance of emerging infectious diseases and the risks of adverse neurodevelopmental outcomes.

By using Early Childhood Development Index data from Demographic and Health Surveys as well as Multiple Indicator Cluster Surveys in 35 low- and middle-income countries, estimates of the prevalence of neurodevelopmental deficits have recently been published, indicating that 14.6% of children had low Early Childhood Development Index scores in the cognitive domain, 26.2% had low socioemotional scores, and 36.8% performed poorly in either or both domains. Risk factors for such deficits should be considered in the context of sensitive time periods in fetal and childhood physical and neurodevelopment. For the purposes of this journal supplement, neurodevelopment is defined as the dynamic interrelationship between environment, genes, and the brain whereby the brain develops across time to establish sensory, motor, cognitive, socioemotional, cultural, and behavioral adaptive functions. This definition has been modified for this effort from an earlier version recently published in Nature.

As will be explored more fully below and throughout this supplement, the implications of potential insults are compounded by their timing (ie, during critical and sensitive periods of neurodevelopment). A sensitive period is a time in development during which the brain is particularly responsive to stimuli or insults followed by an extended period of ongoing responsiveness, but to a lesser degree (eg, language development); by contrast, a critical period refers to a time in development when the presence or absence of an experience results in irreversible change (eg, binocular vision). Figure 1 depicts neural network development from the prenatal period into adulthood, including key time periods, sensitive and critical, for specific domains. An example of the former might be the formation of a healthy attachment between infant and caregiver, which requires an adult who is invested in the child’s needs during the first 2 years of life. An example of the latter is the need to treat children born with cataracts in the first few months of life for children to ever develop normal vision. For most aspects of human behavioral development, the concept of sensitive periods is the most applicable, given the prolonged course of brain development and the enormous range of experiences to which children from different cultures and societies are exposed.

### Table 1 Global Trends in Under-5 Mortality

The global under-5 mortality rate has dropped nearly 53% since 1990, from around 91 deaths per 1000 live births to 43 per 1000 live births in 2015. In 2000, for example, there were 9.8 million annual deaths of children <5 years of age. Pooled estimates for 42 countries that included >90% of all such deaths identified leading causes as:

- neonatal conditions (33%),
- diarrhea (22%),
- pneumonia (21%),
- malaria (9%), and
- HIV (3%)

In 2013, mortality rates reduced to 5.9 million deaths per year with a major shift in the causes:

- preterm birth complications cause 15% of all under-5 deaths and, along with other neonatal causes, represent 44% of all deaths;
- pneumonia (15%),
- diarrhea (9%),
- malaria (7%), and
- AIDS (2%) deaths have declined in relative terms, and even more so in absolute terms.

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**TABLE 1 Global Trends in Under-5 Mortality**

<table>
<thead>
<tr>
<th>Year</th>
<th>Mortality Rate</th>
<th>Causes</th>
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</thead>
<tbody>
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<td>1990</td>
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domains follow sensitive periods, of those that do, most sensitive periods occur during the first few years of life. Importantly, not all sensitive periods are the same, even within the same general domain. For example, the acquisition of syntax likely follows a much more compressed time table than the acquisition of vocabulary, which may extend throughout much of the lifespan. Similarly, the formation of attachments likely follows a different time table than the acquisition of executive functions (i.e., cognitive control), which, like vocabulary, is apt to be broadly tuned.

During sensitive periods, when there is maximal brain plasticity, experiences can “cut both ways.” That is, positive experiences are likely to direct development along a typical trajectory, whereas negative experiences can undermine this trajectory. This association is particularly true if such negative experiences continue beyond the sensitive period. Accordingly, interventions are more likely to be met with success when implemented early, when many brain regions and circuits are at their peak of plasticity. However, effective interventions are also needed throughout the life-course from early childhood through young adulthood to achieve the best possible outcomes for those who did not receive appropriate support at earlier time points. For example, recent advances in understanding the molecular signals that regulate the opening and closing of sensitive periods, such as those reported in animal models by Hensch and colleagues, may prove particularly helpful in developing new “late-onset” interventions.

Although healthy debates continue about the data quality, complexity of causality, and mechanisms involved, multiple lines of evidence link impaired early-life development with later health impairment. Examples that provoke challenging genetic, epigenetic, microbiologic, and metabolomic models for understanding include potential development and metabolic consequences of diseases of poverty, such as repeated enteric infections in early childhood in impoverished areas. The associations of key prenatal factors and being small for gestational age (SGA) with an increased risk of mortality
and subsequent stunting are well recognized.13

**RISK FACTORS FOR IMPAIRED NEURODEVELOPMENT**

The fact that a range of periconceptual, fetal, and postnatal factors affect health and neurodevelopmental outcomes in an interconnected manner is well established. Increasingly, at both the population and individual level, there is a cooccurrence of malnutrition (ie, both overnutrition and undernutrition) and infectious and noncommunicable diseases, each of which has strong nutritional and inflammatory components that impact and are impacted by neurodevelopment, particularly in the context of pregnancy, birth outcomes, infant feeding, and maternal health, including adolescents. A host of environmental factors have been identified in low-resource settings (LRS) that increase the risk for altering the course of neurodevelopment.24,25 Figure 2 illustrates an early adversity causal model of the interactions between early childhood adversity, biological changes, and long-term outcomes.

Specific examples of early-life insults and adversities that are of particular relevance to LRS include:

- Prematurity: Preterm birth, particularly in LRS where fewer interventions and services are available, can lead to both short- and long-term deficits in neurodevelopment,26 including specific impairments in attention27 and higher-order cognitive skills.28 Although multifactorial in origin, prematurity risks include maternal undernutrition, micronutrient deficiencies, as well as subclinical infections and inflammation; these risks may vary in different populations and are affected by genetic influences. Given the prevalence of prematurity in the United States and globally, it is fortunate that some progress on solutions to the health care of such children worldwide has been made,29 such as with recently developed nutritional guidelines for preterm infants.30

- Nutrition: Malnutrition, including both undernutrition and overnutrition, clearly has implications for all aspects of child development. An abundance of evidence exists implicating undernutrition as an independent causal factor in altering physical and neurologic development, with both short- and long-term implications for health and quality of life.31

- Infectious disease and inflammation: It is well known that chronic diarrheal illness, often due to poor sanitation, food safety, and water quality, is associated with chronic inflammation. In a cohort of Bangladeshi infants living in poverty, Jiang et al32 have reported decreased scores on the Bayley Scales of Infant and Toddler Development33 in association with...
febrile illness as a clinical marker of inflammation and a variety of proinflammatory cytokines. This is an impressive demonstration that children experiencing early inflammatory processes are at risk for diminished or delayed development. Whether there is catch-up later in life is unknown.

- Violence: Child maltreatment increases the risk of both adverse neural and cardiovascular outcomes. A recent systematic review of population-based surveys, including data for 96 countries, estimates that 1 billion children ages 2 to 17 years, representing over half of all children globally, experienced violence in the past year. This pervasive exposure to conflict and violence in early childhood can have far-reaching consequences for the physical and mental health of future generations.

- Toxic stress: For the purposes of this article, toxic stress will be defined by using key concepts introduced by the National Scientific Council on the Developing Child, which described toxic stress as being the excessive or prolonged activation of the physiologic stress response systems in the absence of the buffering protection afforded by stable, responsive relationships and the result of cumulative adverse childhood experiences. There is now extensive evidence from neuroscience, molecular biology, and epigenetics illustrating that increases in heart rate, blood pressure, and serum glucose, coupled with elevations in stress hormones and inflammatory cytokines fuel the fight or flight response to deal with acute threat. Furthermore, excessive or prolonged activation of stress response systems can lead to long-term disruptions in brain development, immune status, metabolic systems, cardiovascular function, and gene expression. Animal and human studies have found associations between early-life adversity and toxic stress to changes in brain architecture and gene expression, potentially resulting in long-term and even intergenerational physical and mental health consequences. Importantly, toxic stress is most deleterious to the developing brain when it occurs during a sensitive or critical period of development and may have lifelong effects. Consequently, toxic stress is an important concept with implications for the research, clinical, and policy arenas.

### THE IMPACT OF NUTRITION ON NEURODEVELOPMENT

The evidence to support the intimate and inextricable role of food and nutrition, including in mortality and human development is compelling. Suboptimal nutrition, associated with fetal growth restriction, stunting, wasting, and deficiencies of vitamin A and zinc, along with suboptimal breastfeeding, is associated with ~45% of all deaths of children <5 years of age. The Pelotas cohort of 3500 infants followed up to 30 years of age, adjusted for potential confounders, showed that participants who were breastfed for at least 12 months, as compared with <1 month, scored on average 3.76 points higher on IQ tests, achieved 0.91 extra years of education, and earned higher monthly incomes. These effects are especially notable given the known benefits of exclusive breastfeeding for newborn and child survival and the impacts on the burden of morbidity due to gastrointestinal and respiratory infections. Stunting is included among the 2013 World Health Assembly nutrition targets, but the world is off track for achieving the global target of reducing stunting prevalence by 40% by 2025. As per the latest estimates, the median prevalence of stunting in the 65 countdown countries with data from 2009 or later is 32%, and ranges from 9% in China to 58% in Burundi. Progress in these domains has been relatively slow, despite the calls for action at the World Health Assembly and through The Lancet Undernutrition Series in 2013.

Few countries have launched comprehensive programs integrating child survival and nutrition at scale. A significant advance in recent years is the recognition of the relationship between maternal undernutrition, indeed even preconceptional factors, such as maternal height, and fetal growth restriction, resulting in SGA births. Not only has SGA been shown to compound the risk of neonatal mortality, especially among preterm infants, but it has also been shown to account for at least a fifth of all stunting in children at 18 months of age. This association could be stronger in South Asia, which has significantly higher rates of maternal malnutrition and SGA births. To illustrate, both maternal height and BMI were found to be independently associated with childhood stunting in Pakistan, and similar relationships have been shown from an analysis of data from the National Family Health Survey of India.

Stunting has been associated with impaired cognitive development, effects that are only partially mitigated by schooling. In addition, although the magnitude and duration of effects in the postnatal period and infancy remain controversial, relative to the importance of maternal and fetal effects, some studies have provided intriguing insight into critical opportunities for benefit. In a large study in rural Pakistan with community health workers providing integrated nutrition and child development messaging, although there were developmental benefits at 24 months of age, there was no impact on nutritional outcomes.
However, nutritional intervention in the first 2 years of life has been reported to be associated with as much as a 10% higher IQ score and 46% higher wages in later life.\textsuperscript{53}

Given the close nexus between poverty and undernutrition, it is not surprising that significant correlations between poverty and brain development have been demonstrated.\textsuperscript{54,55} Other research looking at factors associated with neurodevelopment and poverty has focused on the toxic effects of violence, abuse, and exposure to conflict. Data from the recent \textit{Lancet} series on early child development\textsuperscript{56} also suggest that by using conjoint estimates of poverty and stunting, some 200 million children worldwide are at risk for suboptimal development with huge economic costs over their lifetimes and potentially across generations. These data do not, as yet, take into account the number of families and young children affected by violence, abuse, and exposure to conflict. It is now estimated that at least 40% of the global burden of maternal and child mortality lies in countries affected by national or subnational conflict and population displacement.\textsuperscript{57}

The growing knowledge of the biology of typical and atypical child and brain development, and the potential impact of interventions during sensitive periods of brain development may ameliorate the global burden of adversity and risk. The key focus on the first 1000 days of life points to the importance of the period of fetal development, during which the adverse effects on brain development and linear growth are maximal and the potential for interventions is at a maximum.

\textbf{THE IMPACT OF INFLAMMATION ON NEURODEVELOPMENT}

Our appreciation of the interaction between inflammation associated with chronic infection and various aspects of child development has been greatly informed by the recognition of both the prevalence and nature of “environmental enteropathy” (EE).\textsuperscript{58} EE with disrupted intestinal barrier function, intestinal inflammation, and impaired absorptive function is postulated to impair early childhood growth and neurodevelopment. The fact that inflammation during key life periods may play a critical role in affecting nutrition, EE, and development has been well recognized for well over 2 decades\textsuperscript{59} and was convincingly demonstrated in a series of studies in Malawi and Zimbabwe.\textsuperscript{60–62} These indicate that low-grade exposure to environmental pathogens may create an environment of immunostimulation and may relate to changes in the microbiome\textsuperscript{63} or the insulinlike growth factor axis.\textsuperscript{64} In separate studies, children in Kenya or Jamaica who received treatment with the antihelminthic drug albendazole compared with placebo had significantly better growth, fitness, and cognitive function.\textsuperscript{65,66}

Despite surprisingly comparable growth curves in the first few months of life, the fall from the expected growth trajectory from 4 to 24 months of age in children living in impoverished areas of Asia, Africa, and Latin America has been remarkably consistent in decade-plus reviews as well as in current multisite studies.\textsuperscript{3,67} The extent to which stunted growth is a reflection of intestinal parasitic or other infections or is predictive of impaired cognitive development, or that the latter may occur with an EE independent of stunted growth, has been and remains the topic of many studies ranging from work in Guatemala,\textsuperscript{53} the Philippines,\textsuperscript{51} Kenya,\textsuperscript{63} Jamaica,\textsuperscript{64,67} Peru,\textsuperscript{68,69} and Brazil\textsuperscript{70,71} to the current work by the Interactions of Malnutrition and Enteric Infections: Consequences for Child Health and Development consortium.\textsuperscript{72}

Evidence continues to mount that enteric infections and enteric or systemic inflammation in early childhood or prenatally can impair growth and development and perhaps even increase later life associations with obesity, metabolic syndrome or cardiovascular disease.\textsuperscript{22,32,73} Murine models also confirm that infection can impair growth and undernutrition can greatly worsen infection burdens and their growth impairment, documenting a potential “vicious cycle” with such enteric pathogens as cryptosporidium or enteroaggregative \textit{Escherichia coli}.\textsuperscript{74,75} Although stunting may be an increasingly imperfect surrogate for the long-term effects of early life enteric infections, Victora et al\textsuperscript{43} have noted that the height-for-age z score around the second birthday can be the best predictor of “human capital” in terms of educational attainment, economic productivity, and even the weight of future offspring.

Diarrheal illnesses, a surrogate for enteric infections, EE, and stunting or impaired “catch-up growth”\textsuperscript{68} have also been associated with impaired cognitive development. Specifically, the cognitive impairment most affected appears to be semantic (versus phonemic) fluency and higher executive function, somewhat analogous to the cognitive deficits seen in Alzheimer’s disease.\textsuperscript{76} Because of this, a specific allele of the Apo-lipoprotein E (ApoE4), which has been associated with an increased risk of late-onset Alzheimer’s disease, has been examined and, surprisingly, has been found to be protective against the cognitive deficits seen in children with heavy diarrhea burdens.\textsuperscript{77} Table 2 provides some highlights of this seminal research. Taken together, these findings of a potential benefit of the ApoE4 allele in protecting the cognitive development of children (or enteropathy in mice)\textsuperscript{78} with repeated diarrhea or enteropathy in early
childhood (or specific infections in mice) could help explain a potential selective advantage for this ApoE4 allele despite its clear association with an increased risk for Alzheimer’s disease in later life (an effect that has been termed “antagonistic pleiotropy,” or when a single gene controls more than a single trait, ≥1 of which has beneficial and ≥1 of which has detrimental effects on the fitness of the host). Thus, the evolutionary benefit of ApoE4 (perhaps like other genes, such as the sickle cell trait gene) may only persist in the presence of such health threats as diarrhea or enteropathy (or malaria). As conditions improve, one could imagine the changing “evolutionary value” of different traits over time.

The long-term and even transgenerational effects of early childhood infectious, inflammatory, or nutritional challenges increase the human and health system costs. These costs may be compounded by potential epigenetic mechanisms that may be involved, leading to long-term intergenerational effects. Military recruits whose mothers were pregnant with them in the Dutch hunger winter of 1944 to 1945 were more likely to be obese and, in later life, had problems with certain cognitive functions.81,82 Potential mechanisms could involve leptin promoter methylation, which has been shown to occur during postzygotic development in mice and in humans.83 Indeed, leptin promoter methylation has been shown in recruits who were exposed periconceptionally to the Dutch hunger winter.83,84

Thus, translating basic laboratory research and models into relevance to child nutrition, inflammation, and neurodevelopment holds promise for elucidating not only host and microbiome determinants of the metabolic pathways involved, but also potential practical biomarkers of risk. These biomarkers could be used to assess the effectiveness of innovative interventions to optimize these critical determinants in early childhood. The critical roles of the microbiota in influencing susceptibility to (and being influenced by) malnutrition and enteric and other infections are rapidly growing areas of research and are beyond the scope of this overview.85,86 Similarly, relevant metabolic and other biomarkers of intestinal barrier function, microbial translocation, inflammatory and immunologic signaling, and local and systemic inflammation are important areas of research and clinical application.87,88

### Implications for Research, Program, and Policy Development

Based on what we know about the effects of early-life adversity and sensitive or critical periods in development, what should our research priorities be? First, we need to improve our understanding of the dose, timing, and duration of early adversity. For example, which forms of adversity, at which levels, and at which time periods exert the greatest impact on development? Why and how does susceptibility to stress vary with age, especially during sensitive periods of heightened or diminished sensitivity to environmental influences? Are these sensitive periods limited to early childhood or could there be windows of opportunity even later, especially in adolescence or adult life? If this can be established, this information will be critical for developing and targeting interventions. More recently, a systematic review of key interventions that can impact maternal, newborn, and child health and nutrition outcomes has shown the potential of integrating strategies for health, nutrition, and nurturing care across the life course89 with much potential for intergenerational benefits.56

Second, much more needs to be known about how experience is biologically embedded. Acquiring this knowledge will require in-depth research into potential mechanisms that link various stress and protective pathways to tailor interventions to different neural and behavioral systems. To address the burden of impaired neurodevelopment and develop strategies that include an appreciation of individual biological differences, it is critically important to link basic molecular research with complementary translational and clinical research and evidence-based service delivery. Such efforts must include an appreciation of host genetic, microbiologic, metabolic, and environmental (including cultural, family, and community) factors. A systems biology approach and characterization of gene networks in the assessment of neurodevelopmental disorders is emerging as a potential future approach to assessing individual variations in neural network configuration and differential vulnerabilities to neurocognitive deficits.

<table>
<thead>
<tr>
<th>TABLE 2 Potential Role of ApoE4 in Cognition</th>
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<tr>
<td>A specific allele of ApoE4, which has been associated with an increased risk of late-onset Alzheimer’s disease, has been found to be protective against the cognitive deficits seen in children with heavy diarrhea burdens.77</td>
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<tr>
<td>The potential link between ApoE4 and cognition has been extended to targeted transgenic mice expressing the human ApoE4 allele. Findings include:</td>
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<tr>
<td>protected intestinal villus morphometry, improved growth trajectories, and reduced shedding of Cryptosporidium parasites in experimental infections with malnutrition.78</td>
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<tr>
<td>The bridge with basic studies may lie in Colton and Czapiga’s work79,80 showing that:</td>
</tr>
<tr>
<td>these mice exhibit increased expression of cationic amino acid transporter-1 that is responsible for arginine uptake</td>
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Third, it is imperative that we improve our armamentarium of tools that can be used to assess the impact of early adversity. Currently, the most widely used tools are relatively coarse behavioral measures (eg, developmental exams) that lack sensitivity to underlying neural mechanisms, cannot be used easily in life given the infant’s limited behavioral repertoire, and are largely developed in Western, high-resource countries. There are now many more promising models as well as genetic and metabolomic tools available to us that may help us understand mechanisms and develop biomarkers and interventions.

Finally, as mentioned previously, advances in the neurobiology of sensitive or critical periods will likely lead to new discoveries in ways to rescue or reopen these important time periods in brain development. If we were able to rescue a sensitive period later in life, without neural circuitry becoming unstable (ie, sensitive periods may exist in the first place because newly formed neural systems crave stability), then we may be able to develop targeted interventions much later in life that have comparable efficacy to those implemented early in life. Work on all these fronts should vastly improve our knowledge of how to intervene in the lives of children exposed to early-life adversity and must receive adequate support and funding for research. And while we wait for the science to improve the understanding and pathogenesis of neurodevelopmental risks and deficits, we know enough about evidence-based practices that can ameliorate the effect of such adversities during sensitive time periods to prioritize this for action. What is needed is an integrated and accelerated strategy for research in this field that prioritizes action across the discovery, development, and delivery pathways with concomitant investments in monitoring and evaluation.

**ABBREVIATIONS**

- ApoE: apolipoprotein E4
- EE: environmental enteropathy
- LRS: low-resource setting
- SGA: small for gestational age

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