Assessment of Neurodevelopment, Nutrition, and Inflammation From Fetal Life to Adolescence in Low-Resource Settings

Parminder S. Suchdev, MD, MPH,[a,b] Michael J. Boivin, PhD, MPH,[c,d] Brian W. Forsyth, MBChB,[e] Michael K. Georgieff, MD,[f,g] Richard L. Guerrant, MD,[h] Charles A. Nelson III, PhD[i,j,k]

abstract

Efforts to improve child neurodevelopment are critical to health, equity, and sustainable development, particularly in low-resource settings in the United States and globally. The colliding epidemics of food insecurity, infectious diseases, and noncommunicable diseases interact and impact neurodevelopment. Understanding the complex relationships between nutrition, inflammation, and neurodevelopment can inform clinical and public health interventions to improve outcomes. This article reviews key definitions, tools, and considerations for the assessment of nutrition, inflammation, and child neurodevelopment. The effectiveness of existing assessment tools to reflect status and biology, particularly in relation to each other, and to predict long-term changes in health is examined. The aim of this review is to present the extant evidence, identify critical research gaps, and suggest a research agenda for future longitudinal and intervention studies to address the assessment of nutrition, inflammation, and child neurodevelopment, particularly in low-resource settings. Despite research gaps, there is a strong relationship between nutrition, inflammation, environmental factors, and child neurodevelopment, which emphasizes the need to evaluate targeted, early interventions to improve long-term health and well-being.

Departments of [a]Pediatrics and [b]Global Health, Emory University, Atlanta, Georgia; Departments of [c]Psychiatry and [d]Neurology and Ophthalmology, Michigan State University, East Lansing, Michigan; [e]Department of Pediatrics, Yale University, New Haven, Connecticut; Departments of [f]Pediatrics and [g]Child Psychology, University of Minnesota School of Medicine, Minneapolis, Minnesota; [h]Center for Global Health, Department of Medicine, University of Virginia School of Medicine, Charlottesville, Virginia; [i]Laboratories of Cognitive Neuroscience, Boston Children's Hospital, Boston, Massachusetts; [j]Department of Pediatrics, Harvard Medical School, Boston Massachusetts; and [k]Harvard Graduate School of Education, Cambridge, Massachusetts

Dr Suchdev was a panelist at the original *Eunice Kennedy Shriver* National Institute of Child Health and Human Development 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; Drs Boivin, Forsyth, Georgieff, Guerrant, and Nelson were panelists 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.

DOI: 10.1542/peds.2016-2828E

Accepted for publication Dec 21, 2016

Address correspondence to Parminder S. Suchdev, MD, MPH, Department of Pediatrics, Emory University, 1760 Haygood Dr, Atlanta, GA 30322. E-mail: psuchde@emory.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This supplement was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the United States National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

Recent research in a number of fields is shedding light on the complex interrelationships and influence of nutrition and inflammation, among other factors, on child neurodevelopment and long-term health outcomes. Although the etiologies of impaired neurodevelopment are complex, there is growing evidence for the independent and interrelated roles of malnutrition and inflammation on neurodevelopmental delay.[1–3] In addition, important modifiers (ie, both protective and risk factors) of the relationship between nutrition, inflammation, and neurodevelopment need to be considered, including exposure to psychosocial influences and poverty and environmental risk factors, among others.[4,5] Although the relationships between neurodevelopment, nutrition, and inflammation are reciprocal (eg, malnutrition can cause neurodevelopmental delay, but a child with neurodevelopmental delay is also at increased risk of malnutrition), we will focus on neurodevelopment as the outcome of ultimate clinical relevance.

To understand the complex relationship between child neurodevelopment and its modifying factors, accurate and relevant assessment tools are needed that are of use both clinically and programmatically. At the onset, a key challenge is to determine whether there is a gold standard for neurodevelopment and nutritional and inflammatory status because there are no established universal norms across the life course. This article is not intended to be a systematic review of the literature, but instead will: (1) provide an overview of key definitions, tools, and applications relevant to the assessment of child neurodevelopment, nutrition, and inflammation; and (2) identify critical research gaps and priorities.

This article will also build on recently conducted work by the authors, including: the NICHD Biomarkers of Nutrition for Development (BOND)[6] and Inflammation and Nutrition Science for Programs and Interpretation of Research Evidence (INSPIRE)[7] projects, which have been charged with developing guidance on biomarkers of exposure, status, and function for micronutrients and inflammation[6–8]; and the Interactions of Malnutrition and Enteric Infections: Consequences for Child Health and Development (MAL-ED) study, which is evaluating the relationships between enteric pathogens, malnutrition, gut physiology, and cognitive development.[9] Furthermore, this review will focus on assessment in culturally diverse, resource-limited settings around the globe, where the burden of malnutrition and inflammation is the highest.

The vernacular with regard to neurodevelopment, nutrition, and inflammation is complex, so, for the purposes of this article and the others in this supplement, we summarize key definitions and terminology in Table 1. Of note, there is not a clear consensus definition in the literature for several of these terms, because definitions are often based on the perspective of researchers in their respective fields of study. Because this article is meant to be multi- and transdisciplinary, we have attempted to present an inclusive definition of key terminology when possible.

In this article, we define neurodevelopment as the dynamic interrelationship between environment, genes, and 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*.[12] Nutrition is defined as the science of food, the nutrients and other substances therein, their action, interaction, and balance in relation to health and disease, and the processes of ingestion, absorption, use, and excretion.[13] Inflammation is a stereotypical physiologic response to infections, tissue injury, psychological stress, and other insults.[15,16] Additional terms listed in Table 1 will be described in more detail within subsequent sections of this article.

ASSESSMENT OF NEURODEVELOPMENT

Behavioral development is driven by changes in brain development, which in turn are driven by the interaction of genes and experience. In this context, it is easy to see how children in low-resource settings (LRS) might be at risk for falling off a typical developmental trajectory, given the large number of early adverse experiences to which many such children are exposed. Such exposures can negatively impact gene expression, which in turn can impact brain development, which in turn can impact behavioral development. Importantly, if such exposures occur during a critical period of brain development, alterations in both brain and behavioral development may be permanent.[12] This interrelationship not only governs the trajectory of a child's development, but is also important in the assessment of child neurodevelopment. Research conducted in LRS focused on the intersection of nutrition and inflammation and their effects on children's development requires attention to the type of research being conducted, its primary purpose, and the methods used.

For the sake of expediency, this article will focus on tests developed for younger children (birth to 3 years of age), for whom there are a paucity of neurodevelopmental assessment tools. However, similar issues discussed in this article

TABLE 1 Definitions and Terminology

Category	Term	Definition
Assessment tools	Biomarker	Objective measurements of normal biological processes, pathogenic processes, or pharmacologic response to a therapeutic intervention.[10]
Assessment tools	Bioindicator	Sentinel measure of functional change in a medically relevant organ (eg, brain) due to changes in exposure or status in response to an intervention.[11]
Neurodevelopment		The dynamic interrelationship between environment, genes, and brain whereby the brain develops across time to establish sensory, motor, cognitive, socioemotional, cultural, and behavioral adaptive functions.[12]
Nutrition		The science of food, the nutrients and other substances therein, their action, interaction, and balance in relation to health and disease, and the processes of ingestion, absorption, use, and excretion.[13]
Nutrition	Nutritional status	The composition of tissue micro- and macronutrients that reflect the intake and absorption of a diet, which, if "healthy," is sufficient to meet or exceed the needs of the individual, to keep the composition and function within the normal range.[14]
Inflammation		Stereotypical physiologic response to infections, tissue injury, psychological stress, and other insults.[15,16]
Inflammation	APR	An innate body defense, which triggers a sequence of physiologic changes in response to a myriad of stressors, including microbial invasion, tissue injury, immunologic reactions, endogenous cell signaling responses, and inflammatory processes.[7]
Inflammation	APP	Plasma proteins produced by the liver in response to APR; classified as positive or negative reflecting their respective increase or decrease in response to the APR.
Inflammation	Acute versus chronic inflammation	Self-limiting physiologic response to infection or tissue injury versus inflammatory response that fails to regulate itself and contributes to continuation of disease process.[7]
Inflammation	Clinical versus subclinical inflammation	Individual has symptoms of inflammation (eg, fever) versus biochemical signs of inflammation in apparently healthy individuals that may or may not be associated with clinical symptoms.[7]
Inflammation	Environmental enteropathy	Histologic abnormalities of the small intestine driven by environmental factors and associated with nutrient malabsorption and stunting.[17,18]
Inflammation	Toxic stress	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 ACEs.[19]

pertain to tests for school-aged children and adolescents (6–17 years of age), which are more thoroughly reviewed elsewhere.[20–26] Although child neurodevelopment is described in different domains (eg, cognitive, language, executive function, self-regulation, motor, sensory, emotional, and social), it is important to recognize that these domains are overlapping and mutually influencing and are driven by an integrated brain–behavior circuitry. For children aged <3 years, a comprehensive assessment that includes all domains is the most valuable for assessing concurrent abilities.[20] Results, however, may be poorly predictive of future development.[27,28] Generally, there has been less emphasis on executive functions, such as socioemotional regulation, impulse control, and the ability to sustain attention,[21] although these areas of neurodevelopment may be affected by different nutritional deficiencies or inflammatory responses. This relationship may be of significance, for example, when considering the effects of malnutrition, because these children are often described clinically as being apathetic with little interaction with others. Measures of executive function in children as young as 2.5 years have moderately strong correlations with intelligence and achievement scores later in childhood[27,29] and might provide complementary information to the comprehensive developmental assessment.[12] To evaluate neurodevelopment in early childhood, preverbal instruments (eg, behavioral tests, such as elicited imitation or functional electrophysiology like evoked response potentials) allow for assessment during the time period when the brain is most plastic, but also more inaccessible due to child behavior.

Regardless of a child's age, the selection of an instrument should first take into account the specific purpose of the assessment and consideration of which areas of a child's development may possibly be affected.[20] However, the choice of instrument may be complicated by cultural considerations, linguistic variability, caregiver literacy, and the level of training and time commitment required for certain tests as well as their costs and availability. Direct testing of children, for example by using the Bayley Scales of Infant Development,[30] requires extensive training of those administering the test and is time consuming and costly. Moreover, as with many instruments standardized in high-income countries (HIC), some items on the Bayley Scales are not appropriate for children living in some LRS. Conversely, caregiver reports might be subject to biases and affected by the literacy

of those providing the information. Instruments developed in HIC have been standardized and validated for the populations for which they were developed, but these often require translation and cultural adaptation and the actual scores may have little significance when used in low- and middle-income countries (LMIC), except for comparisons within that setting.[31,32] One final consideration relates to how best to obtain age- and sex-adjusted standardized scores for published measures because in-country normative data are typically not available.

There have been a number of instruments developed in LMIC for the specific use within the country in which the instrument was developed, but often such instruments have not undergone rigorous development and validation.[22] One exception to this is the Malawi Developmental Assessment Tool, which underwent years of refinement and development, along with a normative sample of 1560 rural and urban children in Malawi.[33,34] However, such a process typically takes dedicated effort and resources over a period of years, and the end result is a neurodevelopmental assessment that is validated and normed for that population alone. There are studies that have demonstrated differences between cultures in ages of achievement for some milestones,[35–37] which heretofore have precluded the development of standardized instruments that can be used internationally across cultures. Generally, however, these items speak to differences in access (eg, "climbs up stairs") or cultural differences (eg "drinks from a cup"), and although there may be wide ranges of ages of attainment for some items, the differences between cultures for most items are usually small.[38] Ertem and colleagues[38] are presently in the process of developing the International Guide for Monitoring Child Development by standardizing and validating the instrument in 4 countries that are culturally and linguistically different (Argentina, India, South Africa, and Turkey) and including only items that are achieved at similar ages. Moreover, some tests, such as the Cambridge Automated Neuropsychological Test and Battery,[39] depend little on language and may be about as "culture-free" as possible; however, the use of computer administration may be less familiar in some settings. Thus, not just the test but how the test is administered can be influenced by culture.

One of the most significant issues in the measurement of child development in LMIC is whether to adapt tests that are already well-validated in HIC (eg, Bayley Scales of Infant Development, Mullen Scales of Early Learning, MacArthur Communication Developmental Inventory) or to favor the use of tests already well-validated in LMIC (eg, International Guide for Monitoring Child Development). Most developmental assessments evaluate the same core domains, such as gross motor, fine motor, visual–spatial ability, and language. If these domains develop in a universally consistent manner in human children, then this suggests that tests from HIC that evaluate these domains in a valid and consistent manner can be reasonably adapted for evaluating these domains for developmental delays in LMIC. However, if the ecological and cultural context overshadows the more universal dimensions of early child development, then more time and effort should be spent on developing neurodevelopmental measures specific to that context. Consequently, a significant evidence gap includes determining whether there are standardized norms for neurodevelopment by sex that are applicable across cultural, socioeconomic, and geographic locations.

In a recent review, Sabanathan and colleagues[24] describe how child development assessment tools can be used responsibly in LMIC. The "checklist" they suggest includes the following questions: (1) Does the developmental assessment adequately measure all aspects of the domain(s) theoretically affected by the risk factor or intervention; (2) Has the measure been shown to be reliable and valid in the population of interest; and (3) Is the measure sensitive enough in the setting to identify the changes expected? Among the list of instruments they highlight are the Kilifi Developmental Inventory, the Guide for Monitoring Child Development, and the Malawian Developmental Assessment Tool, all instruments that are favored by others. There have recently been a number of review articles that provide extensive descriptions of neurodevelopmental assessment instruments used in LMIC.[20–27,40]

ASSESSMENT OF NUTRITION

Malnutrition has 3 principal constituents: undernutrition (defined by poor growth including underweight, stunting , and wasting), deficiencies in micronutrients, and overweight/obesity. Although nearly all nutrients are important for brain development, some have particularly prominent effects, and their deficiencies confer long-term risks (Table 2). Both fetal and postnatal undergrowth, defined as low weight gain, poor linear growth, or microcephaly reflecting poor brain growth, have been associated with poorer neurodevelopment.[41–43] Recently, weight overgrowth has also been identified as a risk to the developing brain.

Linear growth is measured as recumbent length in children <2 years of age and thereafter as standing height in comparison with sex-specific population reference growth curves. The World Health

Organization (WHO) standard curves demonstrated that children around the world who were breastfed, middle-class, and free of infection grew remarkably similarly, thus establishing an achievable standard goal for growth.[45] "Abnormal growth" has typically been statistically defined as a measurement below or above a given percentile or *z* score for age.

By definition, weight, length, head circumference, and bodily proportionality measures change over time as the child grows. Quality of growth is important to consider in terms of neurodevelopmental risk. The sparing of head growth may be associated with the sparing of neurodevelopmental consequences compared with conditions that compromise head growth. However, the compromise of somatic growth suggests an imminent risk to the brain if conditions do not change. Chronic inflammation and stress result in stunting, whereas linear growth is compromised at the expense of weight. Studies in LRS support the concept that this growth pattern is associated with poorer neurodevelopment.[46] Body composition also changes throughout childhood and can be estimated by low-cost devices, such as skinfold calipers and measuring tape, or accurately measured with expensive tools, such as air displacement plethysmography or dual-energy radiograph absorptiometry.

As with physical growth, there is evidence that many nutritional biomarkers (eg, serum proteins, iron markers, alkaline phosphatase) change with sex and age from the neonatal period through adolescence.[47] Others (eg, retinol, phosphate, calcium) do not. Typically, neonates have lower values of most serum proteins (eg, albumin, prealbumin, retinol binding protein, transferrin), with preterm neonates having the lowest values. Physiologic factors, such as fasting, inflammation, renal function, and pregnancy, are associated with many nutrient biomarkers and need to be accounted for in interpreting data.[48] Multiple organizations, including the Institute of Medicine, US Centers for Disease Control and Prevention National Center for Health Statistics (NHANES), and WHO have compiled reference values for nutrient biomarkers by age.[49] A complete review of the assessment of nutrient biomarkers is outside the scope of this article. Table 3 summarizes some key biomarkers to assess the exposure, status, function, and effect of iron, vitamin A, iodine, B_{12}, folate, and zinc as reported in the BOND and INSPIRE projects.

Ultimately, biomarkers that provide a valid measurement of sufficient, marginal, or deficient nutritional status need to be linked to meaningful health outcomes, in this case neurodevelopment, to be useful in determining whether and when an intervention should occur. Ideally, the biomarker cutoff level should herald "brain risk" as opposed to "brain damage." In the case of growth, interventions to improve nutrient delivery and accretion should be instituted when the weight gain velocity is faltering, before the onset of linear growth suppression and in advance of head circumference compromise.

Cutoff biomarker values that identify brain risk are few and far between for micronutrients that are known to have particularly profound effects on early brain development. Many studies that suggest that a nutrient affects brain development are observational in study design. In these studies, the definition of a nutrient deficiency hinges on population cutoffs, usually the fifth percentile value. Although many of these studies demonstrate an association between a "low" value and poorer neurodevelopmental performance, it remains unclear whether the cutoff from a neurodevelopmental risk perspective might not occur at a value other than the fifth percentile. This conundrum exists because the nutrient status of the brain is largely beyond reach. Biomarkers are measured typically on specimens that are easily obtainable (eg, urine, serum, hair), but may bear little resemblance to brain status.

The problem of relying on statistical cutoffs for a population is shown

TABLE 2 Nutrients With Particularly Prominent Effects on Early Brain Development and Later Adult Function

Category	Nutrient	Evidence for Critical/ Sensitive Period During Neurodevelopment	Early Deficiency Results in Long-term Dysfunction	Evidence for Epigenetic Programming of Brain
Macronutrients	Protein	Yes	Yes	Unknown
	LC-PUFA	Yes	Yes	Yes
	Glucose	No	Yes	Unknown
Micronutrients	Iron	Yes	Yes	Yes
	Zinc	Yes	Yes	Yes
	Copper	Yes	Yes	Unknown
	Iodine	Yes	Yes	Unknown
	Folate	Yes	Yes	Yes
	Choline[a]	Yes	Yes	Yes
Vitamins	A	No	Yes	Unknown
	B_6	No	Yes	Unknown
	B_{12}	Yes	Yes	Unknown
	C	Yes	Unknown	Unknown
	D	Yes	Unknown	Unknown
	E	Yes	Yes	Unknown

This table was adapted from ref 44. See text for details.
[a] Choline is not considered a nutrient.

TABLE 3 Clinically and Programmatically Relevant Biomarkers of Micronutrient Status Adapted from the BOND and INSPIRE Projects

Micronutrient	Biomarker	Type	Clinical Versus Population Use	Advantages	Limitations
Iron[50]	Hemoglobin	Function	Clinical, population	Low-cost, field friendly	Not sensitive or specific for iron status
	Ferritin	Status	Clinical, population	Sensitive for iron deficiency, responds to iron interventions	Increases with the APR
	Soluble transferrin receptor	Status	Population	Less sensitive to inflammation	Less sensitive and specific than ferritin
	Total iron binding capacity	Status	Clinical		Changes only with depleted stores
	Zinc protoporphyrin	Status	Clinical, population	Sensitive measure of iron deficiency, low cost	Impacted by lead, inflammation
	Reticulocyte hemoglobin content	Status, function	Clinical	Measure iron availability to cells	Not validated
	Bone marrow	Status	Clinical	Gold standard	Invasive
Iodine[51]	Salt iodine content	Exposure	Population	Low-cost	
	Urinary iodine	Status, exposure	Population	Useful to monitor trends	Not valid in individuals
	Thyrotropin	Status, function	Clinical	Screening test for thyroid function	
	Thyroglobulin	Status, function			
	Goiter	Function	Clinical, population		Late effect, not specific
Folate[52]	Serum folate			Measure of short-term folate status; highly responsive to interventions	Inconsistent cutoffs
	Red blood cell folate			Measure of long-term folate status; highly correlated with intake	Inconsistent cutoffs
	Plasma homocysteine			Functional biomarker (elevated when folate status is low); responsive to folate interventions	Not specific (elevated with other B-vitamin deficiencies, renal insufficiency, etc)
Zinc[53]	Plasma or serum zinc	Status, function, effect	Population	Used to define population prevalence of deficiency; responds to zinc supplementation	Not a good indicator of individual status; Impacted by numerous factors (eg, inflammation, fasting, sex, age)
	Stunting	Function, effect	Population	Growth response to zinc supplementation reflects preexisting zinc deficiency; Easy to measure	No definitive cutoffs; Surrogate measure
Vitamin A[54]	Retinol	Status	Population	Used to define population prevalence of deficiency	Not a good indicator of individual status; Impacted by inflammation, obesity
	Retinol-binding proteins	Status	Population	Used as proxy for retinol	Not a good indicator of individual status
	Modified relative-dose–response	Status	Population	More responsive to interventions	Requires vitamin A_2 isotope dose and HPLC for analysis
	Retinol isotope dilution	Status	Population	Measure deficiency and excess	Requires 2 blood samples, high-cost
	Dark adaptation	Function	Individual	Responds to vitamin A supplementation in deficient subjects	Requires cumbersome equipment

We have not included dietary assessment, which may be helpful to assess exposure and status for each of these nutrients. HPLC, high-performance liquid chromatography.

in the following example. The fifth percentile for serum ferritin concentration at birth is ~40 μg/L. Serum ferritin is a biomarker that reflects storage iron, and low liver stores of iron are associated with a 30% to 40% loss of brain iron content.[55,56] Newborns with serum ferritin concentrations <40 μg/L indeed have abnormal auditory recognition memory processing.[57] However, other studies using a cutoff

of 76 μg/L (~25th percentile) have demonstrated a variety of abnormal neurobehavioral functions that are plausible based on known functions of iron in the brain.[58–60] The example shows that the population-based fifth percentile value for the nutrient biomarker is likely different from the brain risk bioindicator value. Identifying the ideal biomarkers and their "actionable" cutoff values to preserve brain function constitutes an important future research agenda.

The same conundrum that exists for iron also exists for zinc, iodine, and long-chain polyunsaturated fatty acids (LC-PUFAs). Indeed, whereas there is an extensive battery of tests to assess iron status, the biomarker armamentarium is more limited for these critical brain micronutrients. The critical cutoff for serum zinc or urinary iodine with respect to brain concentrations of functional outputs is not known. The situation is more promising with LC-PUFAs, where animal models have shown that PUFA concentrations in red blood cells closely mimic brain concentrations.[61] Although it is still unknown what red blood cell concentrations in humans would index functionally relevant brain LC-PUFA deficiency, the potential exists for a peripherally measurable biomarker of brain status.

ASSESSMENT OF INFLAMMATION

Inflammation, as characterized by the acute phase response (APR), is an innate body defense activated by a myriad of stressors, including microbial invasion, tissue injury, chronic disease states, immunologic disorders, and psychological stress.[7] The APR begins when activated macrophages release a complex network of cytokines, which then stimulate hepatocytes in the liver to produce acute phase proteins (APPs). Compared with cytokines, which have short half-lives, APPs remain longer in the blood and can be measured to reflect an individual's inflammatory status. The types and function of APPs have been recently reviewed in the INSPIRE project.[7]

Inflammation is associated with numerous adverse health outcomes, including cardiovascular disease,[62] psychiatric and mood disorders,[63,64] and some cancers.[65,66] Inflammatory responses can be characterized as acute (self-limiting and lasting days to weeks) or chronic (failing to regulate themselves and lasting months to years). Inflammation can also be characterized as clinical (individual has clear symptoms of the inciting cause of inflammation) or subclinical (no outward evidence of illness and detected only biochemically based on elevated APPs).[7] Because various stimuli may cause clinical or subclinical inflammation, an individual's inflammatory status may not simply be predicted by a reported history of recent infection or trauma, and biochemical biomarkers of inflammation need to be measured. Furthermore, normal values may fluctuate by age and life course. Although inflammation is generally protective to the host because it removes injurious stimuli and promotes the healing of damaged tissue, overproduction of inflammatory mediators may amplify the APR and contribute to the continuation of chronic inflammation.[15]

Currently, the specific effects of inflammation on neurodevelopmental outcomes remain unknown. Inflammation due to infection can affect the brain directly (eg, meningitis, encephalitis, microstrokes due to malaria) with devastating consequences. For example, cerebral malaria affects subsequent frontal lobe function and academic performance.[67] Generalized or central nervous system–specific infections elevate proinflammatory cytokines, which in turn negatively affect neurodevelopment. Cerebral white matter is at high risk during infectious inflammation because oligodendrocytes are sensitive to the proinflammatory cytokines induced by general or brain-specific infections. Based on the trajectory of white matter development, inflammation in fetal life (termed fetal inflammatory response syndrome) and in the first 2 postnatal years would have the greatest effect on white matter.[68] Neurobehavioral consequences of inflammation-induced hypomyelination include poorer connectivity and slower speed of processing.

Noninfectious processes, such as obesity and psychological stress, also activate many of the same biological processes as infection. In the absence of protective mechanisms, which include coping strategies and healthy interpersonal relationships, a condition known as toxic stress can result from frequent and prolonged activation of the body's stress response systems, resulting in deleterious effects on children's health and development.[19] There is clear evidence that maternal psychological stress alters fetal/neonatal neurodevelopment.[69] Physiologic responses to stress include activation of the hypothalamic–pituitary–adrenocortical axis and sympathetic–adrenomedullary system with resulting increases in stress hormones, such as corticotropin-releasing hormone, cortisol, norepinephrine, and adrenaline, and these changes cooccur with other mediators, including inflammatory cytokines.[19,70] There is growing evidence from both animal and human studies that persistently elevated levels of stress hormones can alter the size and architecture of the developing brain, specifically the amygdala, hippocampus, and prefrontal cortex. The functional consequences of such changes include increased anxiety and impaired memory and

mood control and have been related to subsequent problems in the development of linguistic, cognitive, and socioemotional skills.[71] A recent study of holocaust survivors and their offspring also suggests there can be epigenetic alterations from preconceptual severe psychophysiologic trauma.[72]

The long-term effects of adverse childhood experiences (ACE) have been best documented in the ACE study, a large, on-going, population-based study started in 1995 in the United States.[73] The instrument used in this study is a relatively brief questionnaire obtaining information on 10 different categories of adverse experiences. The results have shown a cumulative dose effect with ≥4 adverse experiences correlating to substantial increases in poor health outcomes. Recently, the ACE International Questionnaire has been developed for global use with the support of the WHO.[74] It includes questions on 13 different categories of adverse experiences and is presently undergoing an evaluation, with early evidence of its validity from a study conducted in Nigeria.[75] More research is needed to additionally characterize the direct effects of inflammation on neurodevelopment and, in particular, interventions that can favorably impact this relationship.

Clinically and programmatically relevant biomarkers of inflammation are summarized in Table 4. Inflammatory biomarkers can be systemic and measured in serum (eg, APPs). Currently, the most frequently measured APPs to assess inflammation are C-reactive protein (CRP) and α1-acid glycoprotein (AGP). CRP rises rapidly and remains elevated for ~1 week after symptom resolution, whereas AGP rises more slowly but remains elevated for several weeks.[76] Recently, high-sensitivity CRP methods have become available, and 5 mg/L has generally become accepted as the upper limit of the normal range.[77] However, lower CRP cutoffs may be useful for detecting acute infection in young children.[78] AGP has been used as a measure of chronic or longer-term exposure to inflammation, but there is some uncertainty as to the threshold that defines "elevated" AGP, especially in relation to the interpretation of nutrition biomarkers.[79]

Tissue-specific inflammatory biomarkers can also assess inflammation locally. For example, in addition to direct assessment of small or large intestinal histopathology or special staining of inflammatory cell subtypes or of tight junction disruption, intestinal inflammation as well as intestinal barrier disruption can be measured by using any of a number of fecal and other biomarkers. Examples of these biomarkers include lactulose: mannitol (or rhamnose or xylose) absorption by measuring these sugars in the urine 2 to 5 hours after ingesting a test dose, or by such assessments as fecal α-1-antitrypsin (to indicate barrier disruption enabling this serum protein to "leak" into the gut lumen). Local intestinal inflammatory biomarkers include fecal lactoferrin, calprotectin, myeloperoxidase, neopterin, or lipocalin, any of which might be associated with evidence of systemic inflammation, assessed using biomarkers such as highly-sensitive CRP or AGP. Additional biomarkers of intestinal or systemic inflammation include intestinal fatty-acid–binding protein, serum amyloid A, CD14, and lipopolysaccharide-binding protein. Other urinary metabolites and measures of inflammation are in development and are outside the scope of this review.

THE INTERACTION OF NUTRITION AND INFLAMMATION: CONSIDERATIONS FOR ASSESSMENT

The interactions between inflammation and nutrition are complex and bidirectional. Nutrition can directly impact immune function and the inflammatory response. This topic is reviewed in detail in the INSPIRE report.[7] In summary, malnutrition in all forms impairs both innate and adaptive immunity, which in turn impairs resistance to and recovery from infections. For example, intestinal permeability is increased in severe protein energy malnutrition, which increases the risk of invasive bacterial disease.[82] Vitamin A and zinc deficiency increase the risk of severe infection and result in ~275 000 child deaths annually, nearly 5% of all child deaths.[83] Although micronutrient supplementation may have beneficial effects on childhood mortality and infectious morbidity (eg, preventive zinc supplementation and reduced incidence of pneumonia and diarrhea),[84] in certain settings, it may also increase the risk of adverse outcomes (eg, iron supplementation and increased malaria morbidity).[85]

Conversely, inflammation can negatively affect nutritional status through several mechanisms, including decreased dietary intake, reduced intestinal absorption, and increased urinary excretion.[86] Additionally, inflammation can directly affect concentrations of nutrients, because some nutrition biomarkers are themselves APPs (eg, serum ferritin and retinol). For example, ferritin is a positive APP and therefore increases in subclinically-infected/inflamed individuals irrespective of iron status.[87] Thus, without taking into account the effects of inflammation on ferritin, the prevalence of low iron stores can be underestimated by 14%.[88] Although high ferritin in noninflamed individuals would suggest iron overload, in settings with inflammation, total body iron is likely normal or low. The anemia is not due to total body iron deficiency, but to functional iron deficiency. Overall, it can be difficult

TABLE 4 Clinically and Programmatically Relevant Biomarkers of Inflammation Adapted From the INSPIRE Project

Biomarker of Inflammation	Normal Range	Settings Where Used	Clinical Versus Population Use	Use in Resource-Limited Settings	Comments
Systemic					
White blood cell count	4–11 000/μL	Acute inflammation (usually infection)	Clinical	Y	Varies by age
CRP[a]	0.001–10 mg/L	Acute, subclinical, chronic	Clinical, population	Y	
AGP	0.6–1.0 g/L	Subclinical	Population	Y	
Erythrocyte sedimentation rate	0–30 mm/h	Acute, subclinical, chronic	Clinical	Y	Increases with age and higher in females
Albumin	35–50 g/L	Acute inflammation (usually infection)	Clinical	N	Decreased during pregnancy
Procalcitonin	≤0.5 ng/mL	Acute inflammation (usually infection)	Clinical	N	
IL-6	Varies	Chronic	Population	N	Potential role in aging; chronic stress
Tumor necrosis factor α	Varies	Chronic	Population	N	Potential role in aging; chronic stress
Serum amyloid A	∼0.01 g/L	Acute	Clinical	N	
Tissue-specific (intestinal, CNS)					
Fecal markers of intestinal inflammation (eg, neopterin, α-anti-trypsin, myeloperoxidase, lactoferrin, calprotectin[80,81]	Varies	Chronic	Clinical, population	N	May predict linear growth; marker of environmental enteropathy, inflammatory bowel disease
Antibodies (eg, anti-LPS)	Varies	Acute inflammation (usually infection)	Clinical	N	Produced in response to infection, vaccination, or from placenta, breastfeeding, injection of antiserum; May modulate neurodevelopment

This table was adapted from ref 7. See text for details. CNS, central nervous system; LPS, lipopolysaccharide.

[a] High-sensitivity CRP may show minor, but potentially important, elevations in the 15- to 30-mg/L range that may be seen with common milder infections, in contrast to the higher levels (>300 mg/L) seen only with major infections or inflammatory processes.

to impossible to interpret total body iron status, much less brain iron status, under these conditions. The Centers for Disease Control and Prevention and WHO recommend measuring inflammatory markers for the assessment of population iron status by using serum ferritin, and to either exclude individuals from analysis who are inflamed, or to raise the cutoff of ferritin to define deficiency.[89,90] However, there are no universally accepted methods for accounting for inflammation in estimating micronutrient status, which can lead to incorrect diagnosis of individuals, as well as over- or underestimation of the prevalence of deficiency in a population.[7,47,87,91] To address these challenges in the assessment of nutrition status, a collaborative research group called Biomarkers Reflecting Inflammation and Nutrition Determinants of Anemia has been formed to pool and analyze data from population-based nutrition surveys and answer priority research questions related to the assessment of micronutrient status in settings of inflammation.[79] Preliminary findings suggest a strong relationship between CRP and AGP and both iron (ferritin, soluble transferrin receptor) and vitamin A (retinol binding protein) biomarkers. A recommended statistical approach to account for the confounding effects of inflammation on these nutrient biomarkers is being developed.

There is a tendency to address nutrient deficiencies as "supply-side" problems, which leads logically to an intervention of giving more of the nutrient in question. Although this may be appropriate in most cases, it is important to recognize that nonnutritional factors influence nutrient status, nutrient biomarker readouts, or both. In the catabolic state of severe infection, macronutrient trafficking and the hormonal milieu in which nutrients operate are likely altered. Counterregulatory hormones, such as cortisol, promote tissue breakdown (eg, glycogen, muscle mass) to provide a ready source of glucose. Relative insulin, insulin-like growth factor 1, and growth hormone resistance ensure that macronutrients are not used for tissue accretion (eg, growth). The subsequent growth slowing with prolonged illness ultimately will affect macronutritional biomarkers,

such as growth, head circumference, and serum proteins.

RESEARCH GAPS AND FRONTIERS

Despite advances in the understanding of the relationships and influence of nutrition and inflammation on child neurodevelopment, important research gaps remain. We summarize key gaps in knowledge related to the assessment of neurodevelopment, nutrition, and inflammation in Table 5 and include studies needed to address these research questions.

A significant gap in the current science of child neurodevelopmental assessment pertains to the lack of valid and sensitive tests of brain/behavior development in young, preverbal children with good predictive validity. Furthermore, the timing of when to assess neurodevelopment may be influenced by the domain of interest and even the child's sex.[92] Understanding whether early assessment predicts later-life functioning is particularly a challenge because neurodevelopment itself is so dynamic. Measures of cognitive and motor development in infants that are sensitive to gestational and perinatal risk factors, and at the same time are predictive for developmental delay and disability later in childhood, are urgently needed. Experimental measures of infant development, such as gaze length for violation of expectancy for physical events[93–95] and neuromotor proficiency in movement and balance,[96] might be good candidate measures for such an infant neuropsychological assessment battery.

An additional significant gap pertains to the development of measures from infancy through middle childhood into adolescence that evaluate the modifying impact of biological and environmental risk and resilience in a consistent and reciprocal manner. Sensitive biomarkers of risk that relate to early child development measures have been documented and additional studies are underway.[97–99] However, the notion of resilience to developmental risk is not well defined or measured for children in LRS.[100] Positive neuroplasticity within the developing brains of children is a double-edged sword, with risk and resilience cutting both ways in the face of genetics and environment.[101] What is needed is a comprehensive model to encompass the genetic, biological, neuropsychological, and social factors of resilience that can be engineered to buffer children against all manner of risk to normal brain/behavior development.[102] Furthermore, we need to understand the predominant forms of child development risk and resilience factors as children develop across the life span from gestation (in utero) through adolescence.

A final gap in child neurodevelopmental testing pertains to its integration with cutting-edge tools that provide a more direct assessment of the brain, bypassing behavior. Such tools possess several advantages. First, because they often do not require a verbal or motor response, they may be more "culture-free" than many behavioral assays used in LRS (particularly those exported from high-resource western settings). Second, particularly in the infancy period, they may permit an evaluation of brain function during a time when the behavioral repertoire is limited. Finally, such tools may shed light on the neural mechanisms that underpin behavior, something behavioral tools cannot do. One such example is a recent seminal publication that used magnetoencephalography brain imaging technology to provide the first evidence of the use of computerized cognitive game training to strengthen the intra- and interhemispheric brain pathways undergirding attention and working memory processes activated by these games.[103] Another example of the potential for the integration of new technologies to child development assessment is that of near-infrared spectroscopy. This technology is a relatively new optical imaging technique that has shown promise in examining child neurodevelopment and therefore potentially has a role in examining the interactions of nutrition, inflammation, and child neurodevelopment. Compared with other neuroimaging techniques, near-infrared spectroscopy has the advantage of being noninvasive, portable, quiet, relatively low-cost, and less sensitive to motion artifacts.[104] Finally, electrophysiological tools, such as the EEG and event-related potentials, have been used for decades to examine the temporal and spatial neural mechanisms underlying a variety of perceptual and cognitive skills.[105–107] The application of these technologies to studies on the effects of nutrition and inflammation on child neurodevelopment in LRS will of necessity depend on the ability to implement and fund the technology.

With the advent of new tools to assess the full effects of specific diets, environments, and microorganisms (including potential pathogens and enteric or other infections) on the metabolism and microbiota of the child, research opportunities emerge to dissect relevant inflammatory and nutritional pathways and develop innovative interventions to optimize neurodevelopment. This work must address the nutrition and inflammation assessment questions listed in Table 5, as well as the need to integrate our understanding of these assessments with full metabolomic studies and long-term follow-up of neurodevelopment in the field. For this work to occur, innovative biomarkers and relevant animal models are needed in which outcomes can parallel more complex nutritional and microbial realities

TABLE 5 Key Research Gaps in the Assessment of Neurodevelopment, Nutrition, and Inflammation

Problem or Question	Studies Needed
Assessment of neurodevelopment	
1. Lack of standardized "norm", by sex, for neurodevelopment that is applicable across cultural, socioeconomic, and geographic contexts.	Large-scale longitudinal study (eg, "WHO growth study for neurodevelopment") that tracks the development of "healthy" children in multiple countries.
2. Lack of valid and sensitive tests of brain/behavior development in infants and young children with good predictive validity.	Preverbal children
3. How frequently should neurodevelopment be assessed during the course of a study?	In a longitudinal study extending over the first decade of life, determine how many data points are optimal (ie, how often should samples be obtained) to accurately create a true developmental picture.
4. Are neurodevelopment indicators stable and consistent over time?	
5. Need cutting-edge tools, including brain imaging, that provide a more direct assessment of the brain, bypassing behavior.	
Assessment of Nutrition	
6. Lack of standardized norms for multiple nutrients from birth to 1 y of age. Do values change over time? Define which measurements of nutrient status are stable from birth to adolescence and which change with age.	Properly powered longitudinal studies of normal concentrations of nutrients (particularly those that have the greatest impact on early brain development), starting with cord blood and tracking through 1 y of age.
7. Lack of defined relationships between cutoff values for specific nutrients and acute brain function (behavior) at specific ages.	Measurement of biologically plausible acute brain/behavior functioning as a function of nutrient biomarker status.
8. Lack of defined relationships between cutoff values for specific nutrients at a given age and long-term brain function (behavior).	Measurement of biologically plausible long-term brain/behavior functioning as a function of nutrient biomarker status in childhood.
9. Need to demonstrate that (1) nutrient biomarkers respond to nutrient interventions and that (2) response of nutrient biomarkers index concurrent changes in brain/behavior status.	Clinical trials
10. Need to identify nutrient driven alterations in brain function that are measureable. The ideal assessment would be specific to the nutrient/metabolite (eg, "signature effect" of iron deficiency). These may vary for a given nutrient by age of the subject.	Discover/develop new biomarkers that are "read outs" of metabolic processes occurring in the brain. This may well use proteomic or metabolomic approaches rather than relying on standard biomarkers that index the nutrient's status. These protein or metabolism changes would reflect brain metabolic alterations induced by the nutrient's metabolic properties.
11. What is the magnitude and duration of the effects of inflammation on nutritional status and nutritional biomarkers? How long after the inflammatory event before the biomarkers become useful indices of nutrition?	Longitudinal studies in children that define which and when commonly used nutritional biomarkers are affected by inflammation, including infectious and noninfectious triggers of inflammation.
12. Is there evidence that type of feeding (eg, own mother's milk versus formula in newborns, grain-based versus not, fish consumption, etc) is associated with neurodevelopment?	
Assessment of inflammation	
13. Need improved measures assessing low amounts of local or systemic acute endotoxin (eg, lipopolysaccharide) exposure.	
14. What is the role of maternal inflammation on the development of the fetus?	
15. What are inflammatory biomarkers that distinguish between appropriate and inappropriate/unregulated inflammation?	
16. What are appropriate cutoffs for APPs that best predict changes in nutrition, neurodevelopment, and other key outcomes?	
17. Need field-friendly and cost-effective inflammatory biomarkers that are standardized across laboratories, especially for readily available samples like urine, stool, or blood.	
18. Do the characteristic patterns of change in APPs differ according to population group and to inflammation etiologies (eg, trauma, infection, subclinical inflammation)?	Longitudinal studies that characterize inflammatory response and type and patterns of largely subclinical inflammation may prove critical to healthy development, especially in LMICs.
Other key issues	
19. Need biomarkers and metabolites that can help identify and integrate pathways involved in key outcomes of nutritional impairment or gut or systemic inflammation.	
20. Need improved understanding of the role of the microbiome on child neurodevelopment.	Mechanistic studies
21. What is the resilience of various biomarkers for nutrition, inflammation, and neurodevelopment?	
22. How responsive are biomarkers to interventions and which are more useful to monitor trends and impact of public health interventions (eg, bioindicators).	
23. What are the most "sensitive periods" over the life course for assessing inflammation, nutrition, and neurodevelopment?	

to confirm hypotheses regarding causality that can then be extended to field trials of targeted interventions.

ABBREVIATIONS

ACE: adverse childhood experience
AGP: α1-acid glycoprotein
APP: acute phase protein
APR: acute phase response
BOND: Biomarkers of Nutrition for Development
CRP: C-reactive protein
HIC: high-income countries
LC-PUFA: long-chain polyunsaturated fatty acid
LMIC: low- and middle-income countries
LRS: low-resource setting
WHO: World Health Organization

REFERENCES

1. Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B; International Child Development Steering Group. Developmental potential in the first 5 years for children in developing countries. *Lancet*. 2007;369(9555):60–70
2. Murray E, Fernandes M, Fazel M, Kennedy SH, Villar J, Stein A. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review. *BJOG*. 2015;122(8):1062–1072
3. Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. *Lancet*. 2012;379(9814):445–452
4. Walker SP, Wachs TD, Gardner JM, et al; International Child Development Steering Group. Child development: risk factors for adverse outcomes in developing countries. *Lancet*. 2007;369(9556):145–157
5. Lake A. Early childhood development-global action is overdue. *Lancet*. 2011;378(9799):1277–1278
6. Raiten DJ, Namasté S, Brabin B, et al. Executive summary--biomarkers of nutrition for development: building a consensus. *Am J Clin Nutr*. 2011;94(2):633S–650S
7. Raiten DJ, Sakr Ashour FA, Ross AC, et al; INSPIRE Consultative Group. Inflammation and Nutritional Science for Programs/Policies and Interpretation of Research Evidence (INSPIRE). *J Nutr*. 2015;145(5):1039S–1108S
8. Combs GF Jr, Trumbo PR, McKinley MC, et al. Biomarkers in nutrition: new frontiers in research and application. *Ann N Y Acad Sci*. 2013;1278:1–10
9. MAL-ED Network Investigators. The MAL-ED study: a multinational and multidisciplinary approach to understand the relationship between enteric pathogens, malnutrition, gut physiology, physical growth, cognitive development, and immune responses in infants and children up to 2 years of age in resource-poor environments. *Clin Infect Dis*. 2014;59(suppl 4):S193–S206
10. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69(3):89–95
11. Raiten DJ, Combs GF. Biomarkers and bio-indicators: providing clarity in the face of complexity. *Sight and Life*. 2015;29(1):39–44
12. Boivin MJ, Kakooza AM, Warf BC, Davidson LL, Grigorenko EL. Reducing neurodevelopmental disorders and disability through research and interventions. *Nature*. 2015;527(7578):S155–S160
13. Lagua RT, Claudio VS. *Nutrition and Diet Therapy Reference Dictionary*. New York, NY: Chapman & Hall; 1995
14. Jeejeebhoy KN, Detsky AS, Baker JP. Assessment of nutritional status. *JPEN J Parenter Enteral Nutr*. 1990;14(5 suppl):193S–196S
15. Calder PC, Albers R, Antoine JM, et al. Inflammatory disease processes and interactions with nutrition. *Br J Nutr*. 2009;101(suppl 1):S1–S45
16. Black PH. Stress and the inflammatory response: a review of neurogenic inflammation. *Brain Behav Immun*. 2002;16(6):622–653
17. Prendergast A, Kelly P. Enteropathies in the developing world: neglected effects on global health. *Am J Trop Med Hyg*. 2012;86(5):756–763
18. Keusch GT, Denno DM, Black RE, et al. Environmental enteric dysfunction: pathogenesis, diagnosis, and clinical consequences. *Clin Infect Dis*. 2014;59(suppl 4):S207–S212
19. Shonkoff JP, Garner AS; Committee on Psychosocial Aspects of Child and Family Health; Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. *Pediatrics*. 2012;129(1). Available at: www.pediatrics.org/cgi/content/full/129/1/e232
20. Fernald LCH, Kariger P, Engle P, Raikes A; World Bank. Examining early child development in low-income countries: a toolkit for the assessment of children in the first five years of life. Available at: http://siteresources.worldbank.org/EXTAFRREGTOPEDUCATION/Resources/444707-1291071725351/ExaminingECDtoolkitFULL.pdf. Accessed June 6, 2016
21. Gladstone M, Mallewa M, Alusine Jalloh A, et al. Assessment of neurodisability and malnutrition in children in Africa. *Semin Pediatr Neurol*. 2014;21(1):50–57
22. Fischer VJ, Morris J, Martines J. Developmental screening tools: feasibility of use at primary healthcare level in low- and middle-income settings. *J Health Popul Nutr*. 2014;32(2):314–326
23. Kammerer B, Isquith PJ, Lundy S. Approaches to assessment of very young children in Africa in the context of HIV. In: Boivin MJ, Giordani B, eds. *Neuropsychology of Children in Africa: Perspectives on Risk and Resilience*. New York, NY: Springer-Verlag; 2013:17–36
24. Sabanathan S, Wills B, Gladstone M. Child development assessment tools in low-income and middle-income countries: how can we use them more appropriately? *Arch Dis Child*. 2015;100(5):482–488
25. Ertem IO; World Health Organization. Developmental difficulties in early childhood: prevention, early identification, assessment and intervention in low- and middle-income countries: a review. Available at: http://

apps.who.int/iris/bitstream/10665/97942/1/9789241503549_eng.pdf. Accessed June 6, 2016

26. Robertson J, Hatton C, Emerson E, Yasamy MT. The identification of children with, or at significant risk of, intellectual disabilities in low- and middle-income countries: a review. *J Appl Res Intellect Disabil*. 2012;25(2):99–118
27. Bradley-Johnson S, Johnson CM. Infant and toddler cognitive assessment. In: Bracken B, Nagle RJ, eds. *Psychoeducational Assessment of Preschool Children*. 4th ed. Mahwah, NJ: Lawrence Erlbaum Associates; 2007:325–357
28. Snow CE, Van Hemel SB, eds. *Early Childhood Assessment: Why, What and How*. Washington, DC: The National Academies Press; 2008
29. Duncan GJ, Dowsett CJ, Claessens A, et al. School readiness and later achievement. *Dev Psychol*. 2007;43(6):1428–1446
30. Bayley N. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: The Psychological Corporation; 2006
31. Greenfield PM. You can't take it with you: why ability assessments don't cross cultures. *Am Psychol*. 1997;52(10):1115–1124
32. Abubakar A, Holding P, van Baar A, Newton CR, van de Vijver FJ. Monitoring psychomotor development in a resource-limited setting: an evaluation of the Kilifi Developmental Inventory. *Ann Trop Paediatr*. 2008;28(3):217–226
33. Gladstone MJ, Lancaster GA, Jones AP, et al. Can Western developmental screening tools be modified for use in a rural Malawian setting? *Arch Dis Child*. 2008;93(1):23–29
34. Gladstone M, Lancaster GA, Umar E, et al. The Malawi Developmental Assessment Tool (MDAT): the creation, validation, and reliability of a tool to assess child development in rural African settings. *PLoS Med*. 2010;7(5):e1000273
35. Ivanans T. Effect of maternal education and ethnic background on infant development. *Arch Dis Child*. 1975;50(6):454–457
36. Keefer CH, Tronick E, Dixon S, Brazelton TB. Specific differences in motor performance between Gusii and American newborns and a modification of the Neonatal Behavioral Assessment Scale. *Child Dev*. 1982;53(3):754–759
37. Lansdown RG, Goldstein H, Shah PM, et al. Culturally appropriate measures for monitoring child development at family and community level: a WHO collaborative study. *Bull World Health Organ*. 1996;74(3):283–290
38. Ertem IO, Dogan DG, Gok CG, et al. A guide for monitoring child development in low- and middle-income countries. *Pediatrics*. 2008;121(3). Available at: www.pediatrics.org/cgi/content/full/121/3/e581
39. Cambridge Automated Neuropsychological Test and Battery (CANTAB). Available at: www.cambridgecognition.com/. Accessed June 6, 2016
40. Semrud-Clikeman M, Romero RA, Prado EL, Shapiro EG, Bangirana P, John CC. Selecting measures for the neurodevelopmental assessment of children in low- and middle-income countries [published online ahead of print September 9, 2016]. *Child Neuropsychol*. doi:10.1080/09297049.2016.1216536
41. Goldenberg R, Hack M, Grantham-McGregor S, Schürch B. Report of the IDECG/IUNS Working Group on IUGR effects on neurological, sensory, cognitive, and behavioral function. *Eur J Clin Nutr*. 1998;52(suppl 1):S100–S101
42. Morris SS, Cogill B, Uauy R; Maternal and Child Undernutrition Study Group. Effective international action against undernutrition: why has it proven so difficult and what can be done to accelerate progress? *Lancet*. 2008;371(9612):608–621
43. Pollitt E, Gorman KS. Nutritional deficiencies as developmental risk factors. In: Nelson CA, ed. *Threats to Optimal Development: Integrating Biological, Psychological, and Social Risk Factors*. Hillsdale, NJ: Erlbaum Associates; 1994:121–144
44. Georgieff MK, Brunette KE, Tran PV. Early life nutrition and neural plasticity. *Dev Psychopathol*. 2015;27(2):411–423
45. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. *Acta Paediatr Suppl*. 2006;450:76–85
46. McDonald CM, Manji KP, Kupka R, et al. Stunting and wasting are associated with poorer psychomotor and mental development in HIV-exposed Tanzanian infants. *J Nutr*. 2013;143(2):204–214
47. Lorenz L, Peter A, Poets CF, Franz AR. A review of cord blood concentrations of iron status parameters to define reference ranges for preterm infants. *Neonatology*. 2013;104(3):194–202
48. Haynes BM, Pfeiffer CM, Sternberg MR, Schleicher RL. Selected physiologic variables are weakly to moderately associated with 29 biomarkers of diet and nutrition, NHANES 2003-2006. *J Nutr*. 2013;143(6):1001S–1010S
49. Pfeiffer CM, Sternberg MR, Schleicher RL, Haynes BM, Rybak ME, Pirkle JL. The CDC's Second National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population is a valuable tool for researchers and policy makers. *J Nutr*. 2013;143(6):938S–947S
50. Burke RM, Leon JS, Suchdev PS. Identification, prevention and treatment of iron deficiency during the first 1000 days. *Nutrients*. 2014;6(10):4093–4114
51. Rohner F, Zimmermann M, Jooste P, et al. Biomarkers of nutrition for development--iodine review. *J Nutr*. 2014;144(8):1322S–1342S
52. Bailey LB, Stover PJ, McNulty H, et al. Biomarkers of nutrition for development-folate review. *J Nutr*. 2015;145(7):1636S–1680S
53. King JC, Brown KH, Gibson RS, et al. Biomarkers of nutrition for development (BOND)-zinc review. *J Nutr*. 2016;146(4):858S–885S
54. Tanumihardjo SA. Vitamin A: biomarkers of nutrition for development. *Am J Clin Nutr*. 2011;94(2):658S–665S
55. Petry CD, Eaton MA, Wobken JD, Mills MM, Johnson DE, Georgieff MK. Iron deficiency of liver, heart, and brain in

newborn infants of diabetic mothers. *J Pediatr*. 1992;121(1):109–114

56. Georgieff MK, Petry CD, Wobken JD, Oyer CE. Liver and brain iron deficiency in newborn infants with bilateral renal agenesis (Potter's syndrome). *Pediatr Pathol Lab Med*. 1996;16(3):509–519

57. Siddappa AM, Georgieff MK, Wewerka S, Worwa C, Nelson CA, Deregnier RA. Iron deficiency alters auditory recognition memory in newborn infants of diabetic mothers. *Pediatr Res*. 2004;55(6):1034–1041

58. Tamura T, Goldenberg RL, Hou J, et al. Cord serum ferritin concentrations and mental and psychomotor development of children at five years of age. *J Pediatr*. 2002;140(2):165–170

59. Amin SB, Orlando M, Eddins A, MacDonald M, Monczynski C, Wang H. In utero iron status and auditory neural maturation in premature infants as evaluated by auditory brainstem response. *J Pediatr*. 2010;156(3):377–381

60. Armony-Sivan R, Eidelman AI, Lanir A, Sredni D, Yehuda S. Iron status and neurobehavioral development of premature infants. *J Perinatol*. 2004;24(12):757–762

61. Innis SM. Plasma and red blood cell fatty acid values as indexes of essential fatty acids in the developing organs of infants fed with milk or formulas. *J Pediatr*. 1992;120(4 pt 2):S78–S86

62. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med*. 2004;351(25):2599–2610

63. Réus GZ, Fries GR, Stertz L, et al. The role of inflammation and microglial activation in the pathophysiology of psychiatric disorders. *Neuroscience*. 2015;300:141–154

64. Furtado M, Katzman MA. Examining the role of neuroinflammation in major depression. *Psychiatry Res*. 2015;229(1-2):27–36

65. Garcia-Anguita A, Kakourou A, Tsilidis KK. Biomarkers of inflammation and immune function and risk of colorectal cancer. *Curr Colorectal Cancer Rep*. 2015;11(5):250–258

66. Rivas-Fuentes S, Salgado-Aguayo A, Pertuz Belloso S, Gorocica Rosete P, Alvarado-Vásquez N, Aquino-Jarquin G. Role of chemokines in non-small cell lung cancer: angiogenesis and inflammation. *J Cancer*. 2015;6(10):938–952

67. Bangirana P, Menk J, John CC, Boivin MJ, Hodges JS. The association between cognition and academic performance in Ugandan children surviving malaria with neurological involvement. *PLoS One*. 2013;8(2):e55653

68. Hofer N, Kothari R, Morris N, Müller W, Resch B. The fetal inflammatory response syndrome is a risk factor for morbidity in preterm neonates. *Am J Obstet Gynecol*. 2013;209(6):542.e1–542.e11

69. Monk C, Georgieff MK, Osterholm EA. Research review: maternal prenatal distress and poor nutrition - mutually influencing risk factors affecting infant neurocognitive development. *J Child Psychol Psychiatry*. 2013;54(2):115–130

70. Johnson SB, Riley AW, Granger DA, Riis J. The science of early life toxic stress for pediatric practice and advocacy. *Pediatrics*. 2013;131(2):319–327

71. National Scientific Council on the Developing Child. Excessive stress disrupts the architecture of the growing brain: working paper No. 3. Updated edition. Available at: http://developingchild.harvard.edu/resources/wp3/www.developingchild.harvard.edu. Accessed August 26, 2015

72. Yehuda R, Daskalakis NP, Bierer LM, et al. Holocaust exposure induced intergenerational effects on FKBP5 methylation. *Biol Psychiatry*. 2016;80(5):372–380

73. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. 1998;14(4):245–258

74. World Health Organization. Adverse Childhood Experiences International Questionnaire (ACE-IQ). Available at: www.who.int/violence_injury_prevention/violence/activities/adverse_childhood_experiences/en. Accessed August 26, 2015

75. Kazeem OT. A validation of the Adverse Childhood Experiences Scale in Nigeria. *Research on Humanities and Social Sciences*. 2015;5(11):18–23

76. Thurnham D, McCabe G. Influence of infection and inflammation on biomarkers of nutritional status with an emphasis on vitamin A and iron. In: World Health Organization. Report: Priorities in the assessment of vitamin A and iron status in populations, Panama City, Panama, 15–September 17, 2010. Geneva, Switzerland: WHO Press; 2012. Available at: www.who.int/nutrition/publications/micronutrients/background_paper4_report_assessment_vitAandIron_status.pdf. Accessed August 26, 2015

77. Thurnham DI, McCabe GP, Northrop-Clewes CA, Nestel P. Effects of subclinical infection on plasma retinol concentrations and assessment of prevalence of vitamin A deficiency: meta-analysis. *Lancet*. 2003;362(9401):2052–2058

78. Wander K, Brindle E, O'connor KA. Sensitivity and specificity of C-reactive protein and $\alpha(1)$ -acid glycoprotein for episodes of acute infection among children in Kilimanjaro, Tanzania. *Am J Hum Biol*. 2012;24(4):565–568

79. Suchdev PS, Namaste S, Aaron G, Raiten D, Brown KH, Flores-Ayala R; BRINDA Working Group. Overview of the Biomarkers Reflecting Inflammation and Determinants of Anemia (BRINDA) Project. *Adv Nutr*. 2016;7(2):349–356

80. Kosek M, Haque R, Lima A, et al; MAL-ED network. Fecal markers of intestinal inflammation and permeability associated with the subsequent acquisition of linear growth deficits in infants. *Am J Trop Med Hyg*. 2013;88(2):390–396

81. Langhorst J, Elsenbruch S, Koelzer J, Rueffer A, Michalsen A, Dobos GJ. Noninvasive markers in the assessment of intestinal inflammation in inflammatory bowel diseases: performance of fecal lactoferrin, calprotectin, and PMN-elastase, CRP, and clinical indices. *Am J Gastroenterol*. 2008;103(1):162–169

82. Brewster DR, Manary MJ, Menzies IS, O'Loughlin EV, Henry RL. Intestinal permeability in kwashiorkor. *Arch Dis Child*. 1997;76(3):236–241

83. Black RE, Victora CG, Walker SP, et al; Maternal and Child Nutrition Study Group. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet*. 2013;382(9890):427–451

84. Yakoob MY, Theodoratou E, Jabeen A, et al. Preventive zinc supplementation in developing countries: impact on mortality and morbidity due to diarrhea, pneumonia and malaria. *BMC Public Health*. 2011;11(suppl 3):S23

85. Sazawal S, Black RE, Ramsan M, et al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. *Lancet*. 2006;367(9505):133–143

86. Bresnahan KA, Tanumihardjo SA. Undernutrition, the acute phase response to infection, and its effects on micronutrient status indicators. *Adv Nutr*. 2014;5(6):702–711

87. Tomkins A. Assessing micronutrient status in the presence of inflammation. *J Nutr*. 2003;133(5 suppl 2):1649S–1655S

88. Thurnham DI, McCabe LD, Haldar S, Wieringa FT, Northrop-Clewes CA, McCabe GP. Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta-analysis. *Am J Clin Nutr*. 2010;92(3):546–555

89. World Health Organization; Centers for Disease Control and Prevention. Assessing the iron status of populations. 2nd ed. Available at: www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/9789241596107.pdf. Accessed August 25, 2015

90. World Health Organization. Serum ferritin concentrations for the assessment of iron status and iron deficiency in populations. Available at: www.who.int/vmnis/indicators/serum_ferritin.pdf. Accessed August 25, 2015

91. Northrop-Clewes CA. Interpreting indicators of iron status during an acute phase response--lessons from malaria and human immunodeficiency virus. *Ann Clin Biochem*. 2008;45(pt 1):18–32

92. Lung FW, Shu BC, Chiang TL, Chen PF, Lin LL. Predictive validity of Bayley scale in language development of children at 6-36 months. *Pediatr Int*. 2009;51(5):666–669

93. Luo Y, Kaufman L, Baillargeon R. Young infants' reasoning about physical events involving inert and self-propelled objects. *Cognit Psychol*. 2009;58(4):441–486

94. Wang SH, Baillargeon R. Inducing infants to detect a physical violation in a single trial. *Psychol Sci*. 2005;16(7):542–549

95. Wang SH, Baillargeon R, Paterson S. Detecting continuity violations in infancy: a new account and new evidence from covering and tube events. *Cognition*. 2005;95(2):129–173

96. Ishak S, Franchak JM, Adolph KE. Perception-action development from infants to adults: perceiving affordances for reaching through openings. *J Exp Child Psychol*. 2014;117:92–105

97. Pickler RH, Wetzel PA, Meinzen-Derr J, Tubbs-Cooley HL, Moore M. Patterned feeding experience for preterm infants: study protocol for a randomized controlled trial. *Trials*. 2015;16:255

98. Hearst MO, Himes JH, Johnson DE, et al; Spoon Foundation. Growth, nutritional, and developmental status of young children living in orphanages in Kazakhstan. *Infant Ment Health J*. 2014;35(2):94–101

99. Strand TA, Taneja S, Ueland PM, et al. Cobalamin and folate status predicts mental development scores in North Indian children 12-18 mo of age. *Am J Clin Nutr*. 2013;97(2):310–317

100. Kvalsvig JD, Taylor M, Kauchali S, Chhagan M. Acknowledging methodological complexity in assessing children in HIV-affected communities in KwaZulu-Natal province, South Africa. In: Boivin MJ, Giordani B, eds. *Neuropsychology of Children in Africa: Perspectives on Risk and Resilience*. New York, NY: Springer-Verlag; 2013:37–67

101. Shonkoff JP, Phillips DA, eds. *From Neurons to Neighborhoods: The Science of Early Childhood Development*. Washington, DC: National Academies Press; 2000

102. Boivin MJ, Wouters H, Giordani B. An introduction to the neuropsychology of African children within a co-constructivist paradigm. In: Boivin MJ, Giordani B, eds. *Neuropsychology of Children in Africa: Perspectives on Risk and Resilience*. New York, NY: Springer-Verlag; 2013:1–16

103. Astle DE, Barnes JJ, Baker K, Colclough GL, Woolrich MW. Cognitive training enhances intrinsic brain connectivity in childhood. *J Neurosci*. 2015;35(16):6277–6283

104. Oliveira SR, Machado AC, Miranda DM, et al. Near-infrared spectroscopy as an auxiliary tool in the study of child development [in Portuguese]. *Rev Paul Pediatr*. 2015;33(2):230–240

105. Nelson CA III, McCleery JP. Use of event-related potentials in the study of typical and atypical development. *J Am Acad Child Adolesc Psychiatry*. 2008;47(11):1252–1261

106. Gervain J, Mehler J, Werker JF, et al. Near-infrared spectroscopy: a report from the McDonnell infant methodology consortium. *Dev Cogn Neurosci*. 2011;1(1):22–46

107. Vanderwert RE, Nelson CA. The use of near-infrared spectroscopy in the study of typical and atypical development. *Neuroimage*. 2014;85(pt 1):264–271

Assessment of Neurodevelopment, Nutrition, and Inflammation From Fetal Life to Adolescence in Low-Resource Settings

Parminder S. Suchdev, Michael J. Boivin, Brian W. Forsyth, Michael K. Georgieff, Richard L. Guerrant and Charles A. Nelson III

Pediatrics 2017;139;S23
DOI: 10.1542/peds.2016-2828E

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Assessment of Neurodevelopment, Nutrition, and Inflammation From Fetal Life to Adolescence in Low-Resource Settings

Parminder S. Suchdev, Michael J. Boivin, Brian W. Forsyth, Michael K. Georgieff, Richard L. Guerrant and Charles A. Nelson III

Pediatrics 2017;139;S23
DOI: 10.1542/peds.2016-2828E