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

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abstract Approximately 1 out of 5 children worldwide suffers from childhood malnutrition or stunting and associated health conditions, including an increased susceptibility to infections and inflammation. Due to improved early interventions, most children even in low-resource settings now survive early childhood malnutrition, yet exhibit continuing evidence of neurodevelopmental deficits, including poor school achievement and behavioral problems. These conditions are compounded in children who continue to be undernourished throughout the adolescent years. At present, these sequelae of malnutrition and infection are of major concern in the adolescent population, given that young people between the ages of 10 and 24 years represent nearly one-quarter of the world's population. Therefore, there is an urgent need to focus on the well-being of this age group and, in particular, on behavioral, cognitive, and brain disorders of adolescents who experienced malnutrition, infection, and inflammation prenatally, in early childhood, and during adolescence itself. Because one-third of all women globally become pregnant during their adolescent years, brain and behavioral disorders during this period can have an intergenerational impact, affecting the health and well-being of the next generation. This article summarizes the current state of knowledge and evidence gaps regarding childhood and adolescent malnutrition and inflammation and their impact on adolescent neurodevelopment, the limited evidence regarding nutrition and psychosocial interventions, and the role of resilience and protective factors in this age group. This overview should help to inform the development of new strategies to improve the neurodevelopmental outcomes of high risk adolescent populations.

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FIGURE 1

Maturation sequence of brain development and changes in gray matter volume during childhood and adolescence.⁵ Reprinted with permission from Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci USA*. 2004;101(21):8174–8179.

Childhood malnutrition is present in ~1 out of 5 children worldwide.¹ Due to improved early treatments, most children now survive childhood malnutrition and other associated childhood illnesses, including diarrhea and serious infections. Among those who have endured into adolescence,² many, especially those in low- and middle-income countries, exhibit continuing evidence of undernutrition, poor health, and higher morbidity rates associated with a history of childhood malnutrition. The rise in obesity globally, especially among adolescents from low- and middle-income countries, has also been attributed in part to childhood malnutrition and inflammation, adding to the health burden of adolescents living in these low-resource settings (LRS). Yet, adolescent health and nutrition have been largely ignored,^{2,3} despite the fact that there were 182 million

young people between the ages of 10 and 24 years in 2010 alone, representing nearly one-quarter of the world's population. There is thus an urgent need to focus on the health and well-being of this age group and, in particular, on behavioral, cognitive, and brain disorders that have resulted from exposure to malnutrition and inflammatory disorders prenatally and in early childhood as well as during adolescence.⁴

Adolescence, the period of transition from childhood to adulthood, is a developmental stage associated with rapid physical growth, hormonal and sexual development, social development, and cognitive and behavioral changes. Underlying many of these changes is the dynamic remodeling of brain structure throughout childhood and continuing during this growth period that may play an important role in dictating how the adolescent brain responds

to new stimuli and incorporates information during its maturation to adulthood (see Fig 1).⁵ Modern neuroimaging techniques have facilitated the identification of the continuing changes and patterns of adolescent brain development and their associations with neurocognition and behavior in human and preclinical studies.⁶ However, more research is needed in this age group to identify which specific neural systems retain plasticity and how interventions may impact the brain of the adolescent. For example, it is known that adolescents are particularly vulnerable to adverse stimuli, such as negative peer pressure, addictions, and sleep deprivation.

Some of the challenges specific to adolescent research involve ethical issues, including consenting, difficulty in capturing data because parental involvement is not always possible, and outreach to adolescents who are no longer part of an established family unit. Context and environmental factors are especially important to document during adolescence (see Fig 2). These issues may be more pronounced in culturally diverse LRS where factors, such as chronic versus acute stress, conflict or political unrest, early marriage and pregnancy, significant child care or work responsibilities, and limited educational or vocational opportunities, may be more prevalent. Importantly, there is a need for standardized and validated metrics to assess the factors that may be most likely to impact adolescent brain and behavioral development and to interact with nutritional factors and inflammation, including the role of social networks, parenting, coping skills, depression, perceived status/worth, stress, previous adverse life events, and substance use, among others. Evidence from both animal models and human studies show sex-specific differences in response to early life experiences^{7,8}

FIGURE 2
Relationships among individual and environmental risk factors, inflammation, nutrition, and neurodevelopment for adolescents in LRS.

therefore, all studies of adolescent neurodevelopment should include members of both sexes.

Although interventions to reduce the adverse effects of early malnutrition and inflammation have traditionally focused on pregnant women and young children, the adolescent period may provide an additional window of opportunity for remediation. Because nearly one-third of all women globally become pregnant during their adolescent years,⁹ interventions during this period of life not only impact the adolescents themselves, but also have substantial effects on the well-being of the next generation. Introducing effective interventions during this stage of development, when life-long health-related behaviors are being established, may serve to limit the known life span and

intergenerational consequences (due to both infectious and noninfectious causes) of these childhood conditions.¹⁰

THE IMPACT OF NUTRITION ON NEURODEVELOPMENT DURING ADOLESCENCE

Malnutrition early in life has been implicated in the subsequent development of cognitive and behavioral impairments in childhood,¹¹ but there are few studies of how early malnutrition affects adolescent outcomes. Inattention, conduct problems, aggression toward peers, depression, school failure, and reduced IQ have all been documented in adolescents with histories of malnutrition present during critical periods of brain development.^{12–20}

Many of these adverse outcomes, including attention problems and cognitive deficits, continue into adulthood and can even persist into the subsequent generation.²¹ These adverse outcomes are not limited to cases of growth stunting or protein–calorie malnutrition, but also include iron and other micronutrient deficiencies during early childhood that are known to similarly impact brain, behavior, and cognition in adolescents.^{22,23}

Interventions targeting individuals with histories of early childhood malnutrition are generally instituted in childhood and have not been shown to fully reverse behavioral and cognitive deficits in adolescence. Nutrition interventions alone provide short-term, but only limited long-term benefits for brain and behavior

functions. However, providing good nutrition in combination with a program of psychosocial and or cognitive stimulation^{24,25} resulted in reduced levels of aggression and better educational achievement in adolescence and in young adulthood. The long-term benefits of these types of interventions, especially combined approaches, are just now being studied in large-scale clinical trials.²⁶ Limitations in assessing the impact of such intervention programs are the limited availability of prenatal, birth, and early childhood records and the consequent inability to distinguish between the effects of low birth weight, acute episodes of malnutrition during the postnatal period, and more chronic malnutrition. Moreover, many studies do not adequately adjust for other factors in the child's environment that may cooccur with childhood malnutrition, including poverty, infection, maternal depression, abuse and neglect, and exposure to toxic stress.

Malnutrition during adolescence itself is common, especially in developing countries²⁷ but effects on the brain, cognition, and behavior are not well-documented in this age group. Similar to the findings from follow-up studies of adolescents exposed to early childhood malnutrition, poor nutrition and food insufficiency during adolescence also appear to increase the risk of poor academic, behavioral, and mental health outcomes.²⁸ These adverse outcomes are also seen in adolescents who are suffering from specific nutrient deficiencies. For example, lower intake of B vitamins and folate was closely associated with increased aggressive and delinquent behaviors in 17-year-old Australian adolescents.²⁹ Intervention programs in adolescents that address specific nutrient deficiencies appear to have better results when adolescents are enrolled for at least 3 months; attention deficits and learning

disabilities appear to benefit the most from this intervention.³⁰

In summary, the brain, behavioral, and cognitive sequelae of childhood and adolescent malnutrition may significantly limit the educational and occupational opportunities of impacted individuals,³¹ and the potential cost to society is great.³² Therefore, there is an urgent need to identify research gaps related to our understanding of the relationships between early childhood malnutrition and neurocognitive, behavioral, and social development of adolescents and to develop the basis for designing and implementing effective interventions to mitigate these outcomes (Table 1).

THE IMPACT OF INFLAMMATION ON NEURODEVELOPMENT DURING ADOLESCENCE

The normal maturation and functioning of the adolescent brain requires several developmental steps, starting during the prenatal period and continuing through adolescence itself.⁵ Numerous studies in both humans and animal models indicate that inflammation, resulting from both infectious and noninfectious causes, can disrupt these developmental processes and lead to impaired cognition and behavior later in life. In animal models, exposure of the fetus to immune activators, such as endotoxins, can lead to lifelong changes in cognition and behavior, partly through activation of the kynurenine pathway.³⁴ In humans, prenatal exposure to infectious agents, such as herpes simplex virus (HSV) type 2,³⁵ *Toxoplasma gondii*,³⁶ and cytomegalovirus,³⁷ have been associated with increased risks of psychiatric disorders in adolescence and early adulthood, particularly in individuals with a genetic predisposition to these disorders. There have been fewer studies of the associations between infection in

the postnatal period and subsequent cognitive impairment, other than for HIV infection (discussed below). In a small cohort, postnatal exposure to cytomegalovirus was associated with an increased rate of cognitive impairment in preterm infants.³⁸ Also, childhood exposure to Epstein-Barr virus was associated with an increased risk of psychotic episodes in adolescents.³⁹ The association between exposure to infectious agents and a decreased level of cognitive functioning is also supported by studies in adults; exposures to HSV type 1,⁴⁰ cytomegalovirus,⁴¹ and *Toxoplasma gondii*³⁹ were correlated with decreased levels of cognitive functioning, particularly in domains associated with memory.

Globally, adolescents represent 2.1 million of the 35 million persons infected with HIV.⁴² Adolescents living with HIV include individuals who recently acquired HIV infection via sexual or other routes in addition to those infected perinatally or through breastmilk. HIV infection can be accompanied by a syndrome of cognitive, behavioral, and motor impairment, collectively known as HIV-associated neurocognitive disorders that run a spectrum from asymptomatic neurocognitive impairment to HIV-associated dementia (also known as AIDS dementia complex). More recently, as individuals infected in childhood have reached adolescence, a new syndrome of adolescent HIV-associated neurocognitive disorders has been recognized and characterized.⁴³

In HIV-infected adolescents, the proinflammatory and other immune effects of the virus are present during a critical period for the refinement of executive control and the development of brain systems involved in learning, language, and complex skills, which occurs against a backdrop of transitioning to independence, risk-taking, and

TABLE 1 Gaps in Knowledge Related to Nutrition and Adolescent Brain and Behavior Function

Problem or Question	Studies Needed
Timing of the insult: How do preconceptional, gestational, and postnatal nutritional status impact development and what are the manifestations during adolescence?	Longitudinal studies are urgently needed, examining the long term effects of malnutrition and inflammation at different stages of early development. ^a
Nutrition requirements: What are the macronutrient (protein) and micronutrient requirements in early childhood and adolescence that promote normal brain development?	Studies of nutrition requirements to support brain development in adolescence are needed.
Extranutritional factors: The individual, family, and societal context of the adolescent can greatly modify the response to early insults, including modifying inflammatory response (see <i>Resilience and Protective Factors</i> section). These considerations are especially important in adolescence.	Studies including translational research need to assess and identify the role of extranutritional factors in modifying inflammation and nutrition effects in adolescents.
Sex differences: Need better characterization of sex effects on linkages between nutrition and brain function/development. Outcomes and interventions need to consider possible sex-specific effects of early insults.	All adolescent studies need to include both sexes.
Undernutrition and obesity: The conditions coexist in adolescents living in LRS and both need consideration in relationship to functional outcome. ³³	Comprehensive studies of adolescent over- and undernutrition are needed in LRS.
Key brain and behavioral outcomes: How is executive control and aggressive behavior impacted by previous and concurrent nutritional factors and inflammation? Important effects in adolescent development with implications for health and mental health.	New methodologies appropriate to field work are needed to study brain function and to improve our understanding of nutrition-related executive control and conduct problems. ^a
Comorbidities: Nutritional deficits may increase the adverse effects of alcohol and substance use/abuse on behavior/brain in LRS (double insults), a particular problem in adolescence.	Cofactors should be included, especially when assessing adolescence.
Accessing other databases: Data from “natural experiments” arising from famine, prolonged and extreme dietary restriction, and epidemics may already be available. These data can potentially provide important information in planning new clinical studies of brain structure and function in adolescents with a history of childhood nutritional deficiencies, infection, and inflammation.	Identifying and accessing databases of existing longitudinal cohorts should be encouraged. Leveraging data from existing data sets will be an important adjunct to new longitudinal and collaborative studies in different geographic settings. ^a
Underlying mechanisms	
1) Epigenetic changes, link between inflammation and malnutrition, as a biomarker of impaired brain and behavior function.	1) Epigenetic studies relating early nutritional deficits with epigenetic changes, including their relationship to inflammation. ^a
2) Translational research allows direct examination of brain in a controlled laboratory setting.	2) Translational studies in animal models are urgently needed to examine mechanisms and causality.
3) Role of exposure to infectious agents in terms of gastrointestinal absorption and nutrient use.	3) Studies of the role of specific infectious agents and the microbiomes.
4) Composition of the intestinal microbiome in terms of gastrointestinal functioning.	

^a Priority area.

possible substance use.^{44–47} HIV neuropathology primarily affects the basal ganglia and cerebral white matter, with substantial neuronal loss in the prefrontal cortical regions. In adolescents, this area is still undergoing myelination and remodeling of synaptic connections, and HIV-related insults to normal developmental processes may lead to impairments in complex mental processing.^{48–50} These effects are manifested as lower verbal scores and reading comprehension, lower school performance, and, in studies from the United States, a higher prevalence of psychiatric disease in HIV-infected adolescents compared with HIV-negative individuals.^{51–53} Furthermore, although antiretroviral therapy can slow these changes in

adolescents, they do not reverse them, suggesting that these changes to brain structures may be permanent.

Given the extent of the adolescent HIV epidemic, there is a critical need for more research on long-term neurocognitive outcomes in this population. Although the many virus-specific effects of HIV cannot be generalized to other conditions, the persistent innate immune response that is a hallmark of HIV infection could serve as a model to study the effects of chronic inflammation on neurodevelopment. Importantly, other noninfectious causes of inflammation, including stress and childhood malnutrition, may also impact adolescent brain development.

The gaps in knowledge related to the interaction of inflammation, whether due to infectious or noninfectious causes, and neurocognitive development in adolescent health are depicted in Table 2. These gaps are related to a number of areas, including the need for appropriate biomarkers for the measurement of exposure to specific infectious agents and immune activation. Such assays need to be appropriate for use in adolescents both in terms of their target organisms and immune components as well as the ability to be applied in health settings where adolescents are likely to receive health information and medical care. For example, of particular importance in terms of adolescence is the role of disease acquired by sexual

TABLE 2 Gaps in Knowledge Related to the Impact of Inflammation on Neurodevelopment During Adolescence

Problem or Question	Studies Needed
What are the CNS structures and pathways susceptible to inflammation-driven changes in adolescents?	Developmental studies of brain structure and functioning relating to inflammation.
What are the function and behavioral consequences of neuroinflammation in adolescents?	Evaluation of the effects of exposure to specific infectious agents at different time points.
What are the specific linkages between biomarkers of infection/inflammation and functional capacity/outcomes in adolescents?	Longitudinal studies to assess normal ranges for serum, CSF, and other biomarkers and whether these change in meaningful ways during adolescence. ^a
Are biomarker–function relationships static or modified by earlier adversity or injuries/deficits?	Prospective cohort studies evaluating long-term effects of exposures.
How do infectious agents (eg, TB, viral, helminths) impact the phenotype of chronic inflammation in adolescents?	Practical methods to identify exposure to specific infectious agents in different environmental settings.
What are the immune cell populations in the CNS that affect neuronal and brain structure/function development during adolescence?	Practical methods to characterize immune cell functioning in different environmental settings. ^a
What is the relationship between non-CNS immune activation (inflammation and adaptive immune cells) and CNS immune activation? What peripheral (non-CNS) immune cell types contribute to neuroinflammation? What are the mechanisms that define the cross-talk between the peripheral and central immune systems?	Better methods to interrogate the CNS immune system.
What are the contributions of T cells and other adaptive immune system components to monocyte/macrophage-driven CNS inflammation in adolescents? What adaptive immune system changes exacerbate/mitigate CNS inflammation?	Better understanding of the adaptive immune system.
Can the study of HIV-associated inflammation and neurocognitive development in adolescents serve as a model for other infections?	Additional studies of the mechanisms of HSV-associated inflammation.
What is the role of other sexually transmitted infections in terms of brain development and adolescent behavior (eg, HSV type 2, <i>Chlamydia</i>)?	Better studies of the role of sexually transmitted infections in brain development.
To what extent does exposure to neurotropic infectious agents earlier in life impact cognitive development in adolescence?	Additional cohort studies of infection and cognitive development.
What are the effects of sex/hormone differences on the immune responses to antigen stimuli and exposures to infectious agents in adolescents?	Improved understanding of the immunobiology of hormones.
Epigenetic regulation of inflammatory pathways needs to be examined in relation to early nutrition; may serve as an important biomarker of poor outcomes.	Additional studies of the role of epigenetic modifications.
How does sleep deprivation or altered sleep schedules (circadian rhythm), which are more common in adolescents, affect inflammation?	Improved understanding of the biology of circadian rhythms.

CNS, central nervous system.

^a Priority area.

activity and close contact, such as infections caused by HSV types 1 and 2, *Treponema pallidum*, Epstein-Barr virus, human papillomavirus, and HIV. In the case of adolescents, these agents are important not only for the well-being of the individual, but also in terms of being able to affect the offspring of adolescent pregnancies.

Previous studies have indicated that immune activation and exposure to infectious agents may be associated with an increased rate of cognitive impairment, cognitive decline, and psychiatric disorders in some populations.⁵⁴ Information is just starting to emerge regarding mechanisms by which exposure to infectious agents can lead to these types of changes in the adolescent period. Areas in which there are interesting preliminary data (but for

which additional studies are needed) include the role of genetic factors in terms of susceptibility to infections as well as the role of infections, nutrition, stress, and other factors in modulating gene expression through epigenetic changes in DNA, for example, the role of DNA methylation⁵⁵ and modifications of DNA-binding proteins, such as histones.^{56,57}

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

Gaps in knowledge related to the interaction of nutrition, inflammation, neurodevelopment, and other influencing factors during adolescence are presented in Table 3. At present, there are data on the

adverse effects of undernourishment and malnutrition on innate and cellular immune function in children, including reduced T-cell primary and memory antibody responses,⁵⁸ a reversal of the T helper/suppressor ratio,⁵⁹ atrophy of the lymph tissues,⁶⁰ and reduced natural killer cell activity.⁶¹ Several recent studies have investigated the effects of malnutrition on immune function, particularly peripheral T cell subsets and mucosal barrier-related inflammation, although these come primarily from the adult HIV literature given the geographic overlap of food insecurity and the high prevalence of HIV in LRS.^{62–64} At present, there is a paucity of similar data on how macro- and micronutrient deficiencies impact inflammation and immune function

TABLE 3 Gaps in Knowledge Related to Interactions of Nutrition, Inflammation, Neurodevelopment, and Other Influencing Factors During Adolescence

Problem or Question	Studies Needed
What are the macronutrient and micronutrient deficiencies/excesses before adolescence that predispose individuals to impaired immune function, inflammation, and susceptibility to infection in different environmental contexts?	Longitudinal studies to assess innate and adaptive immune function in adolescents with a history of micro- and macronutrient deficiencies during childhood.
What are the macronutrient and micronutrient deficiencies/excesses during adolescence that permit/promote susceptibility to infection and chronic inflammation in different environmental contexts?	Studies to assess innate and adaptive immune function in adolescents with ongoing nutrient deficiencies
Are the effects of malnutrition-related immune deficiencies on chronic inflammation in adolescents more severe in some environmental contexts (eg, more consequential in areas with prevalent environmental enteropathy)?	Studies to assess adaptive and innate immune function in adolescents living in areas with a high combined prevalence of malnutrition and environmental enteropathy. ^a
What are the anatomic sites and/or pathologic processes most central to chronic inflammation in undernourished adolescents in different environmental contexts?	
Do pathogenic alterations in the microbiome during childhood persist in adolescence? If so, what are the consequences? Does this differ across environmental contexts?	Practical methods for the measurement of the intestinal microbiome. Need for methods other than stool collection in adolescents. Better characterization of the microbiome–inflammation relationship in different geographic, environmental, and genetic contexts. ^a
What are the characteristics of a “healthy” microbiome in adolescents as compared with children or adults? Does this differ across environmental contexts? What is the role of diet and exposure to antimicrobial agents?	
What are the prevalence and characteristics of an “unhealthy” proinflammatory microbiome in adolescents? Does this differ across environmental contexts?	
What are the prevalence and characteristics of “environmental enteropathy” in adolescents? Does this differ across environmental contexts?	Histologic assessments and studies of nutrient absorption and local immune responses in adolescents with environmental enteropathy.
How do environmental enteropathy and chronic gut inflammation affect macronutrient and micronutrient absorption in adolescents?	
In adolescents with environmental enteropathy, what macronutrient and micronutrient factors exacerbate/mitigate chronic gut inflammation?	
What specific infectious agents infecting during the adolescent period affect cognition and behavior?	Cohort and epidemiologic studies to identify infectious agents in different geographic areas.
Which infectious exposures earlier in life affect cognition and behavior in adolescence? What are the critical earlier time points (prenatal, infancy, childhood)?	Assays for the assessment of exposure to infectious agents at different time points, using methodologies appropriate to the adolescent life style in different socioeconomic settings.
How does exposure to infectious agents interact with other environmental risk factors to generate harmful outcomes during adolescence? What are these other factors (nutritional deficiencies, exposure to toxic substances, social stress)?	
How can the effects of exposures to infectious agents that affect adolescent behavior be prevented and treated?	
Can nonnutrient supplements (eg, bovine serum immunoglobulin, prebiotics, or probiotics) ameliorate enteropathy-related chronic inflammation in adolescents and alter health outcomes in adulthood?	Intervention studies directed at preventing inflammation and subsequent neuropsychiatric outcomes in adolescents.
What compositions of macronutrient and micronutrient supplements are most appropriate in malnourished adolescents to both promote nutritional rehabilitation and reduce chronic inflammation?	Additional dietary studies of adolescents.
What macronutrient and micronutrient factors confer the highest risk of neurocognitive deficits in adolescents during episodes of either acute or chronic inflammation in different environmental contexts?	An improved understanding of the role of micronutrients in immunologic functioning.
How can established methods for the prevention of infections (eg, immunizations, hygiene, and condom use) be applied to adolescents in different settings?	Increased studies of vaccine compliance in adolescents.
What is the role of genetics in terms of susceptibility to infectious diseases and the immune response to specific infectious agents?	Improved understanding of the genetic determinants of the immune response to infection.

^a Priority area.

in the adolescent period and whether these differ according to environmental context.

Nutritional insults before adolescence may have consequences for inflammation and immune function during the adolescent period. Reduced memory T cell development in response to childhood undernutrition may confer less effective antibody production

to later antigen stimuli,⁵⁸ whereas malnutrition or enteropathy due to environmental exposures may predispose individuals to chronic villous changes, reduced barrier function, and inflammation.⁶⁵ How these early insults affect the persistence of inflammation and chronic adaptive immune activation in adolescence is a key area for future study.

The interaction of the mucosal barrier, mucosal immune defenses, and the environment in adolescents is an area in particular need of additional study given the significant inflammatory response in individuals with enteropathy. The overlapping effects of nutritional, environmental, and, in many areas, HIV enteropathy can cause profound changes in villous morphology, absorption, and mucosal permeability.^{65–67}

Environmental enteropathy is common in many tropical regions and is thought to result from a combination of recurrent, transient infections with pathogenic bacteria and altered intestinal microbiota resulting in chronic T cell-mediated enteric inflammation, malabsorption, impairment of mucosal integrity, and reduced expression of antimicrobial peptides.^{65,68-70} These processes can be exacerbated by hypoalbuminemia and bowel wall edema, impaired adaptive immune responses, and reduced mucosal integrity in the setting of malnutrition.^{71,72} The majority of studies on enteropathy have focused on children or adults, and new data are needed on the characteristics and nutritional and immune consequences of this condition in adolescence, particularly in regards to possible age-specific factors, such as shifts in dietary quality or excessive alcohol intake (itself a contributor to mucosal dysfunction).

In addition to changes in gastrointestinal barrier defenses, another area of interaction likely to be relevant to adolescence is at the level of the microflora of the gastrointestinal tract, generally termed the microbiome. Studies in animal models have indicated that changes in the microbiome can be associated with alterations in cognition and behavior, related both to changes in the blood-brain barrier and impulse transmission along the vagus nerve, which is one of the principal connections between the intestinal tract and the central nervous system.⁷³ Another recent study has reported that microbiota from malnourished children can transmit growth failure to mice.⁷⁴ The composition of the microbiome both in humans and experimental animals is impacted by a number of factors, including malnutrition, stress, and exposure to antibiotic agents.⁷⁵ Because the adolescent period is closely

associated with changes in dietary habits and hormones (which may adversely impact moods and stress responsivity), it can be anticipated that there are also alterations in the microbiome in this age group.⁷⁶ Longer-term studies are needed to determine whether these changes to the microbiome are permanent and what their contribution is to the malnutrition-related changes in brain structure and function and behavioral/cognitive phenotypes.

The extent of alterations in brain structure and function during adolescence and their specific role in adolescent-onset psychiatric disorders are just beginning to be understood.^{76,77} Similarly, although evidence suggests that exposure to infectious agents and malnutrition increase the risk of neuropsychiatric disorders and other neurodevelopmental disorders, the mechanisms by which these and other environmental factors interact to define risk at the level of the individual adolescent are not well understood. The difficulty in obtaining biological samples from at-risk adolescents, including multiple fecal and blood samples, is a barrier to investigations in this area, but will be critical for future studies to define the evolution and impact of changes in the immune system, microbiome, and other physiologic factors on neurodevelopment in the adolescent period.

RESILIENCY AND PROTECTIVE FACTORS DURING ADOLESCENCE

In spite of the known associations between early childhood nutrition, infection, and inflammation and later behavioral outcomes in adolescence and later adulthood, it is important to note that a certain number of children exposed to these early risk conditions do not develop adverse outcomes.⁷⁸ There are many factors that make an adolescent resilient, allowing him or her to adapt to the

effects of early stressors rather than being adversely affected, and to reach adolescence without serious neurocognitive and behavioral deficits. Examples of “protective factors” that can mitigate the known adverse impact of early insults include good self-esteem, improved socioeconomic circumstances, reduced exposure to stress and violence, a reduction in maternal depression, positive parenting styles and attachment (including father-child relationships), religious practices, and temperament/personality differences. Three groups of protective mechanisms have been identified⁷⁹: (1) at the individual level (eg, self-esteem, genetic and cognitive factors); (2) at the family level (eg, parenting relationships and parental mental health); and (3) at the society/community level (eg, access to education and health care, peer groups, and social supports). The importance of studying the role of social context (ie, family and community-level processes, including stigma) in promoting adolescent resilience is particularly relevant in (post)conflict zones or in other settings where extreme violence is common.⁸⁰

There are substantial gaps in our understanding of protective factors and resilience in adolescence, and global research addressing risk and resilience and its impact on child and adolescent development is an urgent need.⁷⁹ The exposure of millions of children to early childhood malnutrition, infections, and environmental insults creates an urgent need for studies of resilience and protective factors in disadvantaged populations.²⁶ This point is additionally emphasized in a recent review of risk and resilience in HIV/AIDS-affected children to prevent adverse mental health outcomes,⁸¹ but similar resilience research in school-age children and adolescents exposed to famine and malnutrition is practically

TABLE 4 Gaps in Knowledge Related to Evidence-based Interventions for Adolescents in LRS: From Basic Science and Translational Studies to Clinical Care

Problem or Question	Studies Needed
Most interventions with lasting impact have been instituted during critical periods of development (pregnancy to age 2 years). Does adolescence provide another window of opportunity to mitigate previous adversity/injury and counter the effects of early insults during critical periods of development? Can we also target interventions during this period?	A focus on interventions during adolescence is needed, as this period may represent another window of opportunity in individuals exposed to malnutrition, infection and inflammation in early childhood. ^a
Childhood interventions that combine improved nutrition, cognitive, and psychosocial stimulation have been shown to have a greater benefit than either approach alone when instituted.	Combined approaches have not been tested in adolescence and are urgently needed. ^a
New nutritional interventions, such as Ω -3 fatty acid, prebiotic, and probiotic preparations, may prevent mental health disorders in adolescence. ⁸³	Nutritional intervention studies in childhood with sufficient longitudinal monitoring to observe effects in adolescence.
Epigenetic studies may identify new strategies for intervention and change the concepts of “critical and sensitive periods.”	Assessment of epigenetic changes and other biomarkers, particularly inflammatory, may be able to identify adolescents at greatest risk for (or those protected from) health, cognitive, and behavioral disorders.
Because of the known link between inflammation in pregnancy and adverse fetal outcomes, can adolescent interventions be designed to limit inflammation and prevent or modify the transgenerational effects of early childhood malnutrition?	Studies linking inflammatory processes in high-risk adolescents to teen pregnancy outcomes are needed.

^a Priority area.

nonexistent. Finally, studies addressing adolescent resiliency are especially important in the context of large-scale humanitarian crises, physical disasters, political and social upheaval, and extreme violence, because these conditions are more likely to occur in populations that are already experiencing food insecurity and high rates of infection.

Specific gaps include the need for longitudinal research to better identify the potentially complex associations between early malnutrition and infection exposures and potential protective factors impacting the adolescent. This research needs to include data collection at the individual, family, and societal levels, including ethnic/cultural identity. As noted earlier, an individual's sex may also modify the benefits attributable to any protective factor in specific cultural contexts. Although modern genetic, epigenetic, and neuroimaging techniques may help us to better identify individual variability and characteristics of adolescents displaying greater resilience, studies identifying genetic, epigenetic, and environmental interactions are needed because these may also identify those adolescents who seem to “do better.” The importance of examining resilience to early adverse

exposures and identifying potentially modifiable processes from a broad, global perspective may therefore provide an important approach for advancing our understanding of underlying mechanisms and improving the likelihood of successful interventions. Psychosocial and cognitive interventions may have lasting benefits for the neurocognitive effects of childhood undernutrition and inflammation.^{15,16} However, these studies are limited to small sample sizes and require replication. For example, a Jamaican study of 103 stunted children, ages 9 to 24 months, found that children provided with weekly home visits, including play sessions to improve mother–child interaction, were less depressed, less socially inhibited, and less likely to exhibit oppositional and violent behaviors in adolescence¹⁶ and in young adulthood.⁷⁸

IMPLICATIONS FOR RESEARCH, PROGRAM, AND POLICY DEVELOPMENT

Childhood malnutrition remains a significant public health problem, afflicting an estimated 200 million young children worldwide,¹¹ most commonly in economically underdeveloped countries, but also in impoverished segments of more developed countries. Although the global prevalence of undernutrition

in adolescents is not known, a recent survey of 7 African countries shows rates ranging from 12.6% (Egypt) to 31.9% (Djibouti) and a twofold elevated risk in boys.⁸² This finding suggests that inadequate nutrition is chronic in adolescents, leading to additional challenges in addressing the mental health and developmental consequences of adolescents who experienced early childhood malnutrition. Table 4 summarizes gaps in knowledge related to evidence-based interventions for adolescents in LRS: from basic science and translational studies to clinical care.

Our review of the published literature suggests that interventions may be advantageously focused not only on providing adequate nutrition for all pregnant women and young children, but also on making interventions available for high-risk adolescents in LRS who are undergoing biological and brain changes and have increased nutritional and metabolic requirements. In addition, combining nutrition with cognitive and psychosocial stimulation appears to mitigate not only early childhood consequences of early undernutrition and stunting, but also many of the adolescent consequences of these early insults as well as more recently

acquired malnutrition and/or infectious disease.

Given the problems associated with alterations in cognition and behavior in adolescence, the development of effective preventative and therapeutic interventions is crucial. A major uncertainty is how infectious exposures, nutritional insults, and environmental factors occurring during earlier critical developmental periods affect neurologic structure and function, cognition, and behavior in adolescence. Additional study is also needed to understand which aspects of brain and cognitive development are most susceptible during the adolescent period. Furthermore, the extent to which adolescence can be a period to recover from previous insults with neurologic, cognitive, or behavioral consequences before reaching adulthood is unclear.

Although interventions have been developed for other age groups, the implementation of these interventions in the milieu of the adolescent environment may require modifications. For example, outreach to adolescents who are not living with their families, ethical concerns regarding consenting, the methods of administration of medications and supplements as well as the schedule for immunizations may need to be modified for the adolescent age group. Similarly, dietary modifications to address nutritional intolerance, such as gluten-free and lactose-free diets, require additional evaluation in the context of neurocognitive development and would likely require extensive modifications if they are to be used for adolescent populations in resource-limited settings. These limitations point to the need for additional research on interventions to ameliorate adverse neurodevelopmental effects of previous or contemporaneous inflammatory or nutritional insults as well as the training of clinicians

specializing in neurodevelopmental, psychological, and cognitive problems in the adolescent population.

It is still unclear, however, whether interventions introduced only during adolescence are capable of reversing effects sustained during critical periods of brain development. Providing such programs during early childhood and additionally in adolescence may arrest potential developmental cascades by actively supporting subsequent educational and adaptive success. Additional research is therefore needed to link adolescent outcomes with studies of nutritional and social interventions that may ultimately impact public policy. These data will provide a broad perspective on the life-long burdens of early malnutrition and infection on its victims, their families, and their offspring as well as insight into potential protective factors. Given the global significance of these issues, addressing the research gaps described above will have widespread public health implications and impact. Furthermore, gains achieved in the adolescent period may have the additional benefit of positively impacting future generations, because the reproductive years may begin during this developmental stage.

ABBREVIATIONS

HSV: herpes simplex virus
LRS: low-resource setting

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