


REVIEW ARTICLE

Perinatal and early childhood biomarkers of psychosocial stress and adverse experiences

Alejandra Barrero-Castillero^{1,2,3,4}, Lara J. Pierce^{3,4,5}, Saul A. Urbina-Johanson³, Laura Pirazzoli³, Heather H. Burris^{6,7} and Charles A. Nelson^{3,4,8}

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The human brain develops through a complex interplay of genetic and environmental influences. During critical periods of development, experiences shape brain architecture, often with long-lasting effects. If experiences are adverse, the effects may include the risk of mental and physical disease, whereas positive environments may increase the likelihood of healthy outcomes. Understanding how psychosocial stress and adverse experiences are embedded in biological systems and how we can identify markers of risk may lead to discovering new approaches to improve patient care and outcomes. Biomarkers can be used to identify specific intervention targets and at-risk children early when physiological system malleability increases the likelihood of intervention success. However, identifying reliable biomarkers has been challenging, particularly in the perinatal period and the first years of life, including in preterm infants. This review explores the landscape of psychosocial stress and adverse experience biomarkers. We highlight potential benefits and challenges of identifying risk clinically and different sub-signatures of stress, and in their ability to inform targeted interventions. Finally, we propose that the combination of preterm birth and adversity amplifies the risk for abnormal development and calls for a focus on this group of infants within the field of psychosocial stress and adverse experience biomarkers.

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IMPACT:

- Reviews the landscape of biomarkers of psychosocial stress and adverse experiences in the perinatal period and early childhood and highlights the potential benefits and challenges of their clinical utility in identifying risk status in children, and in developing targeted interventions.
- Explores associations between psychosocial stress and adverse experiences in childhood with prematurity and identifies potential areas of assessment and intervention to improve outcomes in this at-risk group.

INTRODUCTION

For over 20 years, there has been increasing evidence that basic brain architecture is established early in life through a complex interplay of genetic and environmental influences.^{1,2} Social experiences shape brain structure and function, particularly during early critical or sensitive periods of development.^{3–5} As a result, experiences encountered from the perinatal period through the first few years can influence development in a manner that persists across the lifespan.⁶ Positive experiences often affect development positively, whereas adverse experiences may elevate the risk of atypical development, which in turn could have life-long consequences.^{7,8} Chronic and cumulative exposure to adversity may increase the risk of negative cognitive, psychosocial, behavioral, and physical health outcomes,^{1,6,9–11} and the biological embedding of these experiences might even influence outcomes in future generations.² Historically, marginalized groups in society have

disproportionately high exposure to adversity. When experienced early in life, such exposures might lead to maladaptive changes that can perpetuate disparities over time.^{9,12–14} How experience becomes biologically embedded, in multiple organ systems, and the identification of biomarkers of psychosocial stress and adverse experiences in childhood remains limited—especially for experiences that occur in the perinatal period and the first years of life.^{6,15} However, valid and reliable biomarkers of psychosocial stress and adverse experiences hold the promise of identifying children at risk of long-term negative outcomes that arise as a result of such experiences early in life, while at the same time illuminating underlying mechanisms. Identifying risk “early” is critical for facilitating effective and specific interventions targeted (a) at the developing systems that are most affected; (b) for the children who are most at risk; and (c) during developmental windows when physiological system malleability increases the likelihood of intervention success.

¹Department of Neonatology, Beth Israel Deaconess Medical Center, Boston, MA, USA. ²Division of Newborn Medicine, Boston Children’s Hospital, Boston, MA, USA. ³Division of Developmental Medicine, Boston Children’s Hospital, Boston, MA, USA. ⁴Department of Pediatrics, Harvard Medical School, Boston, MA, USA. ⁵Department of Psychology, York University, Toronto, ON, USA. ⁶Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA. ⁷Division of Neonatology, Children’s Hospital of Philadelphia, Philadelphia, PA, USA. ⁸Harvard Graduate School of Education, Boston, MA, USA. [✉]email: abcastil@bidmc.harvard.edu

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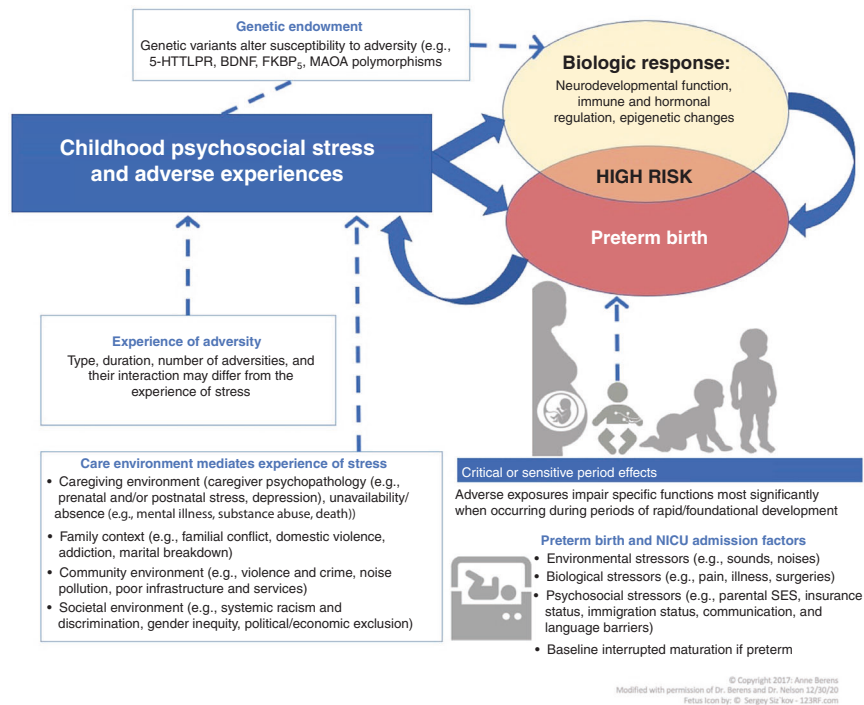


Fig. 1 Conceptual model of how childhood psychosocial stress and adverse experiences may amplify risk for abnormal development, particularly in preterm infants who have additional risk factors. Dashed lines show factors that may mediate the experience of stress and contribute to a difference in susceptibility to adversity including the care environment, the interaction with the genetic endowment that may influence an individual's biologic response, and timing of the exposure during critical or sensitive periods of development where adverse exposures may have a more significant effect. NICU neonatal intensive care unit, SES socioeconomic status.

Despite the growing evidence that psychosocial stress and adverse experiences during childhood have long-term consequences, the definition and dimensions of adversity and adverse experiences remain unresolved.^{10,16} The number, timing, type, and duration of exposures, as well as individual variation, intrinsic characteristics, and developmental status (e.g., born at term or preterm) may affect perception and responses to psychosocial stress and adverse experiences. These responses may affect the lifetime risk of developmental and overall health outcomes.^{1,6,10,16,17} For instance, an individual may be exposed to many stressors and adversities in life but not have a “toxic stress response” which is the response to such stressors that cause a chronic activation of the stress response systems and can disrupt brain development and other systems in the absence of adequate adult support.^{10,16}

The Adverse Childhood Experiences (ACE) Study is a landmark study launched in 1995 and the first to describe in a longitudinal cohort the strong and direct association of adversities during childhood, such as physical and sexual abuse, substance abuse in the household, and the increased lifetime risk of disease and leading causes of death in adults.⁹ Since that integral study, researchers have additionally assessed how not only the number of events experienced, but also the nature and timing of reported events, degree of the physiological stress response may contribute to developmental/health outcomes in different ways.^{18–20} For this review, we have chosen our terminology to extend beyond the ACEs descriptor to explicitly account for the interacting facets of psychosocial stress and adverse experiences that are predicted to elicit a physiological stress response. We included exposures such as physical or mental violence, abuse or neglect, discrimination/racism, and accumulated burden from poverty and economic hardship/ low-socioeconomic status (SES) without adequate social support, that might produce a “toxic stress response”.^{1,6,21} We noted specific experiences reported in the research, and the age

of exposures whenever possible to facilitate differentiation between types and exposure periods.

COMPOUNDING PRE-EXISTING FAMILY STRESS WITH ADVERSITY OF PRETERM BIRTH

Most of the work on psychosocial stress and adverse experiences early in life has focused on the first years of childhood with less work on the prenatal and perinatal aspect. While prenatal exposures influence infant developmental outcomes (e.g., maternal conditions like diabetes, exposure to toxicants, alcohol, tobacco, and substance abuse) less is known about prenatal and perinatal exposure to psychosocial stress and adverse experiences, particularly in preterm infants. Globally, preterm birth (delivery before 37 weeks of gestation) affects ~11% of births worldwide (~10% in the US).^{22–24} Despite medical advances, preterm birth remains a leading cause of morbidity and mortality in children under 5 years of age.^{25,26} Many factors have been associated with an increased risk of preterm birth (e.g., smoking, maternal age, multiple births, spacing between pregnancies); however, most preterm births occur without a known risk factor.²² Preterm birth in the US is more common among Black than White birthing people (14.1% versus 9.1%).²⁷ Historically disparities in birth outcomes had been attributed to biological or genetic variation. However, there is now strong evidence that disparities are largely due to the cumulative effects of structural racism leading to socioeconomic disadvantage, environmental toxicant exposure, and psychosocial stress.^{28–30}

While preterm birth may arise from exposure to psychosocial stress and adverse experiences, it can be a source of stress in its own right. The stress experienced by parents and infants when the earliest days or months are spent in the Neonatal Intensive Care Unit (NICU) warrants exploration as a risk factor for ongoing development (Fig. 1). NICU admission adds levels of psychosocial stress and

adverse experiences (e.g., environmental stressors such as alarms, bright lights, lack of consistent access to a caregiver, biological stressors from pain and necessary life-saving procedures, and financial pressures from hospital bills and lost wages to a baseline level of neurological and physiological immaturity). We conceptualize the NICU as a necessary, but adverse exposure, that compounds the high baseline psychosocial stress and adverse experiences that many NICU families already endure.

LANDSCAPE OF BIOMARKERS ASSESSED IN THE PERINATAL PERIOD AND EARLY CHILDHOOD

Though a full review of adult biomarkers is beyond the scope of the present manuscript, we note that considerable work has reported associations between exposure to adverse childhood experiences and biomarkers in adulthood.^{9,31–33} This body of work provides critical evidence that psychosocial stress and adverse experiences influence physiology in the long term. In our present narrative review, we explore the landscape of biomarkers in early childhood, which have received less attention, and which may differ from biomarker expression observed in adulthood in important ways. With these considerations, the aims of this review are to (a) explore the landscape of biomarkers of psychosocial stress and adverse experiences in the perinatal period and early childhood (up to ~5 years); (b) explore and highlight potential benefits of identifying at-risk infants early, while considering whether different sub-signatures of toxic stress might inform more targeted interventions; (c) discuss forthcoming challenges of using biomarkers in clinical settings with varying resources; (d) discuss concerns regarding how to interpret individual differences and exposures to multiple types of adversity; and (e) propose directions for future research and areas of opportunity, including the proposal that preterm birth acts in tandem with psychosocial stress and early adversity to amplify risk for abnormal development. There is limited research in this last area, but we highlight ways that psychosocial stress and early adversity might interact with preterm birth, indicating a particular need to focus on infants born preterm when identifying stress and adversity biomarkers (Fig. 1).

We define a biomarker as a biological tool that can be quantified, measured, or evaluated to indicate differences in response to psychosocial stress and adverse experiences, and that is expected to be modulated as a result of intervention. Historically, biomarkers may aid in screening, diagnosis, prognosis, or biologic response measurement. An acceptable biomarker needs to be both sensitive in detecting risk and reliable across time, with variability reflecting individual differences in the physiological response to stress.³⁴ Additionally, for clinical use, biomarkers would ideally be affordable and non-invasive (e.g., saliva, urine, skin cells, blood collected for clinical use). For this review, we include all biomarkers that have been associated with psychosocial stress and adverse experiences (as described above), including non-conventional biomarkers of brain function (e.g., those identified using electroencephalography (EEG)).

Psychosocial stress and adverse experiences in childhood can impact multiple systems. Animal and human models demonstrate changes in brain structure and function, chronic inflammation, reduced immunity and autoimmunity (immune dysfunction), premature aging and mortality, and poor health outcomes that arise from chronic and metabolic disease.^{6,9} We reviewed recent studies from PubMed searching for terms associated with psychosocial stress and adverse experiences and individual biomarker terms. We included recent studies and reviews in humans published in English in children ≤5 years of age (see Supplementary Fig. 1 for search strategy). We present biomarkers in different systems and organs, including 1. Biomarkers of brain structure and function, 2. Biomarkers of neuroendocrine function,

and 3. Biomarkers of immune function. Table 1 summarizes the benefits and limitations of each biomarker reviewed.

Biomarkers of brain structure and function

Tools that have been used to assess associations between early psychosocial stress and adverse experiences and neurodevelopment during infancy and early childhood primarily include magnetic resonance imaging (MRI), electroencephalography (EEG), and functional near-infrared spectroscopy (fNIRS).

Magnetic resonance imaging (MRI). Studies using MRI have revealed critical information about the impact of early exposure to psychosocial stress and adverse experiences on the developing brain. Given that MRI is feasible but challenging to perform without sedation during infancy and early childhood, and that sedation, even if minimal, may present some risks,³⁵ the majority of studies have retrospectively examined how structural and functional changes in adolescence and adulthood are associated with adverse experiences that happened early in life.^{36,37} A body of work examining associations between psychosocial stress and adverse experiences and neurodevelopment in infancy and early childhood (i.e., from the neonatal period up to 6 years)³⁸ has revealed that prenatal, and early postnatal experiences (e.g., poverty, abuse/neglect, maternal depression, etc.), including preterm birth,^{39,40} are associated with global reductions in white matter integrity and myelination,^{41,42} changes to brain volume, cortical thickness,^{43–45} and functional networks,⁴⁶ as well as structural and functional alterations to brain regions that contribute specifically to the stress response system (i.e., hippocampus, amygdala, prefrontal cortex).^{47–50} Effects from maternal prenatal stress exposure are also seen in preterm infants as early as term-equivalent age.⁵¹ These neurodevelopmental changes map onto patterns observed later in life.^{36,37}

Electroencephalography (EEG). EEG is relatively inexpensive and well-tolerated by even very young infants, compared to MRI (described above). Although EEG provides relatively poorer spatial localization compared to MRI and does not allow for structural analyses, EEG does provide a readout of cortical function and can be used to probe network-level disruptions in neural development.^{52,53} Critically, analyses of both baseline and task-related EEG power, functional connectivity, and event-related potentials (ERPs) have revealed that early adverse experiences are associated with perturbations in the developing EEG that underlie later cognitive, language, and socioemotional outcomes.^{53–55}

Several distinct EEG patterns have been observed within baseline and task-based EEG. For example, a pattern of elevated power in low-frequency bands (e.g., delta and theta) alongside concomitantly reduced power in high-frequency bands (e.g., beta and gamma) has been observed in children exposed to psychosocial adversity,^{56,57} as well as in children from low-SES backgrounds,^{58–60} and those exposed to high levels of maternal stress (both self-reported and physiological, as measured by cortisol).^{61,62} This pattern may reflect delayed maturation, and associations have been observed between white matter architecture, EEG rhythms,⁶³ and performance on cognitive tasks.⁵⁹ Low gamma power in particular, especially at frontal electrode locations, has also been associated with low-SES status, poverty, and maternal stress.^{58,59,61,64–66} Critically, (frontal) gamma power from as early as the neonatal period appears to predict performance on language and cognitive measures throughout childhood.^{59,67–70} Furthermore, differences in functional neural networks and functional connectivity patterns, particularly cross-gamma and cross-alpha coupling, have been associated with exposure to early psychosocial stressors, suggesting that communication between local and long-distance brain regions may be impacted by certain adverse experiences that occur early in life.⁷¹

Table 1. Summary of projected benefits and limitations of biomarkers of psychosocial stress and adverse experiences in the perinatal period and early childhood.

Biomarkers	Benefits/positive findings	Limitations
Biomarkers of brain function and activity	<p><i>Magnetic resonance imaging (MRI):</i></p> <ul style="list-style-type: none"> - Understand structural and functional changes - Potential available read in the prenatal period (fetus) and after birth 	<ul style="list-style-type: none"> - Need of sedation in some cases to obtain good images - Might not be available at every institution, hard to implement in community/rural locations/at scale - Expensive - Still under study
	<p><i>Electroencephalography (EEG)/functional near-infrared spectroscopy (fNIRS)</i></p> <ul style="list-style-type: none"> - Relatively affordable and well-tolerated by young infants - Easy to use from the earliest stages of development (newborns, including preterm infants) - Measures reflect processes and cortical readouts that are proximal to neurodevelopmental change with potential to identify children at risk - Efficiently and reliably may be collected from a large number of infants/children within a clinical setting - Potential adaptation and use in non-clinical settings (e.g., at home or community with mobile systems) 	<ul style="list-style-type: none"> - No structural information - Less ability for localization of specific brain areas - Still under study, early in the research process, particularly for fNIRS
Biomarkers of neuroendocrine function	<p><i>Hypothalamus–pituitary–adrenal-axis (HPA)</i></p> <ul style="list-style-type: none"> - Well known that glucocorticoids are released under the influence of stress - Glucocorticoids can be easily accessed through hair, saliva, and other easily accessible bodily samples 	<ul style="list-style-type: none"> - More research is required to standardize paradigms for eliciting the stress response, both when the stressor occurs and when the sample is collected influence findings - Some bodily samples are able to capture the nature and timing of certain stressors more than others
Biomarkers of immune functioning	<p><i>CRP and cytokines</i></p> <ul style="list-style-type: none"> - Available research overall indicates that the association between adversity exposure and immune functioning emerges already in infancy - CRP and cytokines can be easily measured from blood and saliva 	<ul style="list-style-type: none"> - Limited number of studies and the inconsistencies between some of the findings hinders the use of inflammation as a biomarker of adversity exposure - Further research is required to elucidate whether these effects can be captured prenatally, how stable these effects are in childhood, what is the best marker (or combination of marker) to collect as index of chronic low-grade inflammation - Lack of age-group specific thresholds (cutoffs) for each marker - Measurement of inflammatory stress response via saliva is a more feasible way to collect samples, however, its study is more recent and still represent many challenges. Most studies measure inflammatory markers in blood, which is a good marker of systemic inflammation, saliva samples might be easier to collect, however, they might represent more local inflammation in the oral cavity.

In the socioemotional domain, a considerable body of work has found associations between patterns of frontal alpha asymmetry (FAA) and both psychosocial stress and adverse experiences⁷² and maternal depression.⁷³ FAA is thought to be associated with temperamental approach/avoidance behavior in infants and children and is predictive of later development of mood disorders such as depression and anxiety.^{74–76} Features of the EEG have also been associated with preterm birth, and interactions between preterm birth and exposure to psychosocial stress and adverse experiences warrant further investigation.⁷⁷

There is also evidence that certain ERP components of the EEG provide a readout of neural processing that is influenced by early experience and maps on specific sensory and cognitive domains as well. Adverse experiences in childhood (e.g., stress, poverty, malnutrition) have been associated with perceptual/sensory development and cortical maturation, as reflected by reduced amplitude and increased latency of the visual (VEP) and auditory (AEP) evoked potential components.^{78,79} Experiences associated

with living in a low-SES context (as measured by parental income or education levels), or exposure to maternal psychosocial stress and adverse experiences early in life are also associated with diminished selective attention and attention allocation (particularly in the auditory domain),^{80–87} and differences in error/reward processing,^{88,89} executive function,^{90,91} and emotional processing of faces.^{92–94} Some of these effects are mediated by factors such as maternal sensitivity⁸⁸ and sympathetic nervous system activation of the child,⁸⁰ and in some cases, appear to be moderated by differential genetic susceptibility (i.e., 5-HTTLPR polymorphism).⁸¹

Functional near-infrared spectroscopy (fNIRS). The majority of studies reporting associations between early psychosocial stress and childhood adversity with neurodevelopment have used MRI and EEG, yet increasing evidence supports the use of fNIRS as a tool for evaluating early neurodevelopment. While fNIRS has been used as early as the neonatal period to reveal the influence of experience on neurodevelopment,⁹⁵ some studies deployed in

low- and middle-income countries are beginning to see adversity-related perturbations in the fNIRS signal later in life as well. For example, a study in rural India used fNIRS in children (4–48-months) to demonstrate that early adverse experiences were associated with brain network activation underlying visual working memory.⁹⁶ In a study of children (6 and 36-months) in Bangladesh, maternal education, maternal stress, and caregiving environment were associated with the magnitude of a neural response to social stimuli.⁹⁷ While the use of fNIRS in this context is in its early days, this tool is relatively affordable and easy to administer in a wide range of contexts, making it a promising emerging tool to understand how early psychosocial stress and adverse experiences shape the developing brain. However, more research is needed before its deployment for clinical purposes.

Biomarkers of neuroendocrine function

Hypothalamus–pituitary–adrenal-axis (HPA). Dysregulation of the HPA axis in response to early life and chronic stress has been studied and reviewed at length.^{98–100} Under the influence of stress, the HPA axis is activated and releases glucocorticoids, cortisol, and derivatives, into the bloodstream. Glucocorticoids can be measured across development from saliva, hair, nails, and other fluids (e.g., plasma). These samples are relatively easy to collect and, thus, provide promising biomarkers for assessing HPA functioning in pediatric populations. However, the timing of sample collection (e.g., measuring basal levels of cortisol vs. cortisol awakening response) and the timing of stress (e.g., acute stress best captured by saliva vs. chronic stress best captured by hair) must be addressed when interpreting HPA axis biomarkers.^{101,102}

Despite the extensive literature, a recent meta-analysis across 14 vertebrate species, including humans, only supported small-to-moderate effects of maternal distress on offspring glucocorticoid levels.¹⁰³ This could be explained by various studies yielding seemingly contradictory results, as both hyper- and hypo-activation of the HPA axis have been found in response to early psychosocial stress and adverse experiences.^{104,105} Hyper-activation of the HPA axis may suggest an acquired resistance to glucocorticoid negative feedback, while hypo-activation may suggest attenuated stress reactivity or an exaggerated suppression of the axis with chronic stress.^{106,107} Both have been found in response to early psychosocial stress and adverse experiences and predict downstream stress-related chronic illness.¹⁰⁸

The effects of early psychosocial stress and adverse experiences on the HPA axis appear to be impacted by the age at which these events were experienced and the sex of the offspring.^{109–111} Some studies suggest an interaction whereby the sex of a fetus moderates maternal cortisol at certain points in pregnancy.¹¹² However, variation in the timing of the stress response, and the stress paradigm used, could explain varying results. Although studies using physical stressors have produced consistent cortisol increases in young infants, studies using psychosocial stressors have produced mixed or null results.¹¹³ A recent meta-analysis on psychosocial stress paradigms and cortisol responses in infants <18-months found the normative response to be small, even when controlling for age.¹¹⁴ As such, more research is essential to tease apart methodological noise from differential effects of early psychosocial stress and adverse experiences on the HPA axis.

Biomarkers of immune function

Exposure to early psychosocial stress and adverse experiences has been associated with an increased risk of psychiatric and medical conditions later in life. Alteration of the immune system has been suggested as one of the biological mechanisms mediating this relationship.^{6,115,116} Chronic exposure to psychosocial stress and adverse experiences leads to chronic low-grade inflammation, which is also aided by the concurrent downregulation of anti-inflammatory pathways such as the HPA axis.^{14,117,118} The link between early psychosocial stress and adverse experiences and inflammation was

initially identified in adults who were exposed to such experiences during childhood and had increased baseline levels of inflammatory markers like C-Reactive Protein (CRP) and pro- and anti-inflammatory cytokines.^{116,119,120} Maintaining a pro-inflammatory state due to early psychosocial stress and adverse experiences has been additionally associated with metabolic dysfunction later in life, increasing the risk of immunosuppression (linked to increased risk of infections and cancer) as well as chronic and metabolic diseases in adulthood (i.e., cardiovascular risk, diabetes, obesity).^{6,115,116,121} A meta-analysis of 25 studies showed the associations of childhood trauma with CRP and two pro-inflammatory cytokines (IL-6 and TNF- α) to be small yet significant.¹¹⁶

While most studies have examined associations later in life, a few have examined the association of psychosocial stress and adverse experiences with inflammation in children <5 years (including infants).¹²² A study determining the association of low-SES, maternal psychosocial stress, depression, and familial stress in infancy showed an association with increased salivary CRP and a composite measurement of pro-inflammatory cytokines (e.g., IL-1 β , IL-6, IL-8, and TNF- α) in 17-month-old children.^{123,124} In Tanzania, a study demonstrated that increased levels of CRP in infants (1–10 months) was associated with lower maternal education and maternal depression.¹²⁵ Another study, also in Tanzania, found that maternal experiences of intimate partner violence during the previous 12 months were associated with increased CRP levels in children ages 6 months to 5 years of age.¹²⁶ However, other studies in 3–5-year-old children found no association between psychosocial stress and adverse experiences and CRP.¹²⁷ Only some variables measured (number of recent and lifetime contextual stressors and traumatic life events) were positively associated with increased salivary interleukin (IL-1 β).¹²⁷

Approaching the question from a different perspective, Riis et al. investigated how psychosocial stress and adverse experiences impact the regulatory mechanisms of inflammation in 5-year-olds and found that maternal distress (measured by depression, anxiety, and parenting stress index) moderates the relationship between cortisol and pro-inflammatory cytokines (IL-1b, IL-6, IL-8, TNF-a).¹²⁸ As levels of distress increased, the relationship between cortisol and cytokines shifted from negative to positive, supporting the idea that chronic inflammation associated with adverse experiences is also explained by less efficient regulation of anti-inflammatory mechanisms.

A recent meta-analysis of studies of children and adolescents found effect sizes for CRP and IL-6 to be similar in magnitude as those reported in adult studies, but associations were not statistically significant.¹²⁹ While data suggest that effects are stronger in infancy and adolescence, the authors invite caution when interpreting these findings, given the limited number of available studies and the heterogeneity in methodological approaches.

PROJECTED BENEFITS OF RECOGNIZING INDIVIDUAL DIFFERENCES IN RISK

Focusing on exposures that occur during critical or sensitive periods prenatally and in early childhood is essential to prevent lasting effects throughout the lifespan.³ The biomarkers reviewed herein may inform our understanding of neurodevelopmental and physiological changes and help predict long-term negative health and developmental outcomes, mainly if measured early and longitudinally. Many of these biomarkers can be collected in an efficient, reliable, and impactful way prenatally, in nurseries or the NICU after birth, in pediatric clinics, and even at home with mobile technology.

In addition to identifying precise mechanisms and individual indicators of risk for adverse outcomes, biomarker analysis can begin to identify different sub-signatures of toxic stress—namely, whether different types of early exposures lead to different types of physiological change in different sub-groups. Identifying

markers associated with very specific exposures, or categories of exposures will help develop more specific and targeted interventions for families.^{16,130} Nonetheless, we recognize that the resolution of disparities will ultimately require large-scale structural changes to reduce exposure to psychosocial stress and adverse experiences among populations facing discrimination and barriers in access to resources and social supports.

FORTHCOMING CHALLENGES AND LIMITATIONS OF THE USE OF BIOMARKERS IN THE CLINICAL SETTING

It remains unknown whether there are specific periods of development during which exposure to psychosocial stress and adverse experiences is most deleterious, and whether this varies by type of exposure or outcome measured.¹⁷ Concomitantly, some conceptual models have suggested that cumulative exposure to multiple adverse experiences over time may influence development more profoundly than acute exposures alone, regardless of their timing.¹³¹ Given the difficulty in separating types of adversity, since many occur concurrently, few studies have compared these factors directly to determine each unique influence and their interaction.

We have included a wide range of potentially negative experiences (e.g., accumulated burden from poverty, abuse, neglect, maternal mental health issues, etc.). However, we know that different experiences might impact development in different ways and that not every child exposed to the same experience will have the same response; perception of stressors, support/resources (extrinsic in the case of environmental context, intrinsic in the case of differential genetic susceptibility), and resiliency tools to overcome exposure to these events vary. Thus, it is difficult to interpret individual differences in physiological responses and, in turn, how to “treat” or intervene.

Another key limitation in research to date is that the identification of generalizable biomarkers requires large and diverse samples. Even when able to include diverse samples, there are still vulnerable and isolated groups with additional barriers to research participation, including indigenous populations, undocumented immigrants, refugees, and asylum seekers, that may have experienced different types of psychosocial stressors and extreme adversity.

Once biomarkers have proven to be reliable, feasible, and highly predictive, another factor to consider is that the availability of tools varies across settings. Collection of blood, saliva, or urine samples may be widely implemented across contexts, however in some remote locations ability to run assays on physiological samples might be limited. Neuroimaging tools are becoming more portable and have been used effectively in very low-resource settings; however, restrictions still exist in terms of cost and ease of access for the most vulnerable populations. Moving forward, the combination of tools will be critical to determine how to identify children at risk and uncover underlying mechanisms that lead to long-lasting effects on health and development. Finally, ethical considerations are paramount when incorporating the use of biomarkers to assess risk into clinical practice (e.g., making sure biomarkers are equally available for all and when risks are identified, interventions to improve outcomes must be promptly deployed).^{132–134}

DIRECTIONS FOR FUTURE RESEARCH AND AREAS OF OPPORTUNITY

Biomarkers of epigenetic change (Accelerated telomere shortening and DNA methylation)

In addition to the biomarkers reviewed, associations between psychosocial stress and adverse experiences, and biological aging has received recent attention, though predominantly in older children and adults. In particular telomeres, or repeating segments

of noncoding DNA that serve as protective caps at the ends of chromosomes and help maintain chromosomal integrity,¹³⁵ have been found to shorten with each cell division contributing to aging and disease in humans.^{136,137} Accelerated shortening may be due to higher oxidative stress and inflammation affecting telomerase activity.¹³⁸ Telomeres are easily collected from saliva or blood^{139,140} and although more research is required to standardize TL assessment, TL is a promising biomarker. In addition to being linked to health, longevity, and chronic diseases, TL has been associated with psychosocial stressors and adverse experiences (e.g., family violence and disruption, discrimination, and racism).^{141–145} According to a large meta-analysis, telomere heritability could be as high as 70%, contributing to intergenerational transmission of stress exposure.¹⁴⁶ Recently, accelerated telomere shortening has been studied in the context of stressors in the perinatal period and early childhood adversity.^{147–153} While shorter telomeres have been associated with various psychological and physiological health ailments in adults, further research is required to determine whether TL at birth and/or in infancy can predict TL later in life.

DNA methylation may also be used to obtain as a marker of aging that may explain intergenerational transmission of stress.¹⁵⁴ However, most studies have been conducted in adult populations. Recently, multidisciplinary teams have been working on developing accurate and non-invasive methods to assess biological aging by using mathematical models to characterize an “epigenetic clock” that can measure and predict biological age, including in children. In the future, this clock may help to evaluate the impact of psychosocial and environmental factors on child development by revealing how gene expression is modified as a result of psychosocial stress and adverse experiences and, as a result, how these modifications impact health outcomes in the long term.¹⁵⁵

Preterm birth and NICU environment as a critical avenue for future research

Considerable research has explored the influence of preterm birth on development^{156,157} and the exposure to biological stress (i.e., from pain).¹⁵⁸ However, little work to date has explored the interaction of familial psychosocial stress and adverse experiences that pre-dated the preterm birth with adversity that resulted from the preterm birth. Together these stressors likely affect developmental and health outcomes¹⁵⁹ which may be modified by identifying infants and families “at risk” and targeting tailored early interventions inclusive of parental education, support and follow up programs.^{160,161} Admission to the NICU offers an opportunity to assess risk, study biomarkers within other studies assessing neurodevelopmental outcomes, and to design interventions to empower families and support infant neurodevelopment.¹⁶²

Other areas of opportunity

In the future, studies may consider performing economic evaluations to assess the cost of incorporating biomarker screening in the clinical setting and the cost of early interventions for children at risk versus the potential cost of the consequences of toxic stress in adult life (e.g., chronic and metabolic diseases in adulthood). Several questions remain regarding the biological embedding of early experiences with long-term development and the clinical use of biomarkers in the perinatal and early childhood period. More studies are needed—particularly longitudinal studies with larger sample sizes and diverse demographic representation.

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AUTHOR CONTRIBUTIONS

Dr. Alejandra Barrero-Castillero conceptualized the review and wrote the initial manuscript. Dr. Alejandra Barrero-Castillero, Dr. Lara Pierce, Mr. Saul Urbina-Johanson, and Dr. Laura Pirazzoli performed a detailed literature review of biomarkers of adversity, edited the manuscript, and critically reviewed it. Dr. Heather H. Burris and Dr. Charles A. Nelson critically reviewed and edited the manuscript for important intellectual content and contributed to the interpretation of findings. Dr. Charles Nelson mentored Dr. Barrero-Castillero throughout the review. All the authors together defined the scope of the review, interpreted the data, and edited the manuscript. All authors approved the final submitted version.

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COMPETING INTERESTS

The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Alejandra Barrero-Castillero.

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