

Leveraging the Biology of Adversity and Resilience to Transform Pediatric Practice

Jack P. Shonkoff, MD,^{a,b,c,d,e} W. Thomas Boyce, MD,^f Pat Levitt, PhD,^{g,h} Fernando D. Martinez, MD,ⁱ Bruce McEwen, PhD[†]

Advances in science are fundamentally changing the way we understand how inextricable interactions among genetic predispositions, physical and social environments, and developmental timing influence early childhood development and the foundations of health and how significant early adversity can lead to a lifetime of chronic health impairments. This article and companion article illustrate the extent to which differential outcomes are shaped by ongoing interactive adaptations to context that begin at or even before conception and continue throughout life, with increasing evidence pointing to the importance of the prenatal period and early infancy for the developing brain, the immune system, and metabolic regulation. Although new discoveries in the basic sciences are transforming tertiary medical care and producing breakthrough outcomes in treating disease, this knowledge is not being leveraged effectively to inform new approaches to promoting whole-child development and preventing illness. The opportunity for pediatrics to serve as the leading edge of science-based innovation across the early childhood ecosystem has never been more compelling. In this article, we present a framework for leveraging the frontiers of scientific discovery to inform new strategies in pediatric practice and advocacy to protect all developing biological systems from the disruptive effects of excessive early adversity beyond providing information on child development for parents and enriched learning experiences for young children.

In 2012, the American Academy of Pediatrics (AAP) published a technical report and policy statement urging pediatricians to play a leadership role in addressing toxic stress in young children.^{1,2} Although these documents embraced a broad eco-bio-developmental framework, their content was focused largely on the brain because of its predominant role in mediating responses to the environment, regulating the stress response, and accounting for the consequences of its activation. Growing scientific understanding of reciprocal interactions among neural, immune, metabolic, and other developing

systems³ now underscores the need to focus more broadly on multisystem influences to better understand the biology of healthy development, the origins and treatment of disease, and the implications for pediatric medicine, advocacy, and research.

These new discoveries highlight the importance of communication across biological systems as they “read” environmental signals and influence each other’s activity through complex feedback loops that are sensitive to a variety of challenges.⁴ Scientific advances are also generating a deeper understanding of the heterogeneity of

abstract



^aCenter on the Developing Child and ^bHarvard Graduate School of Education, Harvard University, Cambridge, Massachusetts; ^cHarvard Medical School and Boston Children’s Hospital, Boston, Massachusetts; ^dDepartment of Social & Behavioral Sciences, Harvard T.H. Chan School of Public Health, Harvard University, Boston, Massachusetts; ^eDepartment of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts; ^fDepartments of Pediatrics and Psychiatry, University of California, San Francisco, San Francisco, California; ^gThe Saban Research Institute, Children’s Hospital Los Angeles, Los Angeles, California; ^hKeck School of Medicine, University of Southern California, Los Angeles, California; ⁱAsthma and Airway Disease Research Center, The University of Arizona, Tucson, Arizona; and [†]The Rockefeller University, New York, New York

[†]Deceased

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Address correspondence to Jack P. Shonkoff, MD, Center on the Developing Child, Harvard University, 50 Church St, 4th Floor, Cambridge, MA 02138. E-mail: jack_shonkoff@harvard.edu

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early factors driving wellness and disease risk on the basis of individual differences in response to a variety of challenges and their developmental timing.⁵

This article and companion article,⁵ provide a framework for leveraging the frontiers of 21st-century biology to catalyze new strategies in pediatric practice and advocacy to protect developing biological systems from the disruptive effects of excessive adversity. The proposed approach is based on an interactive gene-environment-time framework, which is described in more detail and illustrated graphically in the companion article. It underscores the extent to which health and development are shaped by ongoing interactive adaptations to context (at the molecular, cellular, organ, system, and behavioral levels) that begin at or even before conception and continue throughout life, with increasing evidence pointing to the importance of the prenatal period and early infancy for the developing brain, the immune system, and metabolic regulation. The underlying plasticity that influences adaptive capacities (which decreases over varying time lines for different systems) can lead to a wide range of outcomes shaped by inextricable interactions among genetic predispositions, physical and social environments, and age. Variation in sensitivity to context provides a powerful explanation for why some children appear to be more susceptible to hardships or threats than others and why those who demonstrate greater sensitivity are often the most responsive to well-matched interventions.^{6,7}

EARLY CHALLENGES, VARIED ADVERSITIES, AND THE FOUNDATIONS OF LIFELONG HEALTH

Two categories of influence on the health and development of young children elicit considerable attention in the context of pediatric primary care. The first is growth-promoting

challenges that are essential for building resilience. These include separation and individuation, adjusting to new social situations, immunizations against infections, and coping with mild illnesses. The second category of influence includes a wide range of adverse experiences or exposures that can undermine the foundations of health, learning, and behavior. These include the socioeconomic hardships of poverty (eg, food insecurity, unstable housing), the structural inequities and interpersonal discrimination of racism, the psychosocial threats of child maltreatment and community violence, the interactive challenges of maternal depression and parental addictions, the physiologic disruptions of air pollution and other environmental toxicants, the metabolic consequences of poor nutrition, and the developmental effects of extreme prematurity, severe illness, or chronic disability.⁸ Significant adversity, especially early in life, is the strongest known predisposing factor for the most common (and most expensive) chronic health conditions affecting adults, including obesity, cardiovascular disease, diabetes, depression, addictions, and malignancies.^{9,10} As potential growth-promoting challenges become more difficult to master, they move into the realm of increasingly pathogenic influences that can undermine adaptive biological capacities and increase the risk of lifelong illness.

As causal links between adverse childhood experiences and their long-term consequences become better defined, it is essential to recognize that the concept of toxic stress, which was a major focus of the 2012 AAP technical report and policy statement, refers to excessive and/or prolonged stress system activation, not to the source or nature of any specific stressor. The National Scientific Council on the Developing Child, in collaboration with the FrameWorks

Institute, coined the term “toxic stress” in 2005 to describe excessive and/or dysregulated physiologic responses to adversity in young children that can lead to impairments in learning, behavior, and both physical and mental health.¹¹ Four years later, the term first appeared in the peer-reviewed literature, accompanied by a call for a rethinking of health promotion and disease prevention by focusing on the long-term effects of early adversity.¹² Seven years after the term was first introduced, the AAP technical report and policy statement on toxic stress called for a rethinking of the practice of primary care pediatrics to address this issue.^{1,2}

As described in the original working paper, the term toxic stress was initially formulated as one element within a conceptual taxonomy that named 2 other types of stress responses in young children (positive and tolerable) on the basis of postulated differences in their potential to cause enduring biological disruptions.^{11,13} Understanding this critical distinction between growth-promoting challenges and pathogenic adversity lies at the heart of the trusting relationship between pediatricians and parents or other caregivers that drives primary health care in the early childhood period.

Positive stress is defined as moderate, short-lived, physiologic responses (eg, brief increases in heart rate, mild elevations in stress hormone levels) that are turned on when needed and turned off when not needed. These responses help build resilience by providing an opportunity to learn healthy responses to adversity. Central to the concept of positive stress is the availability of a responsive adult who helps the child manage normative stressors (eg, dealing with frustration, novel situations that can be frightening), thereby providing an opportunity to develop effective coping skills.

Tolerable stress refers to physiologic responses (eg, immune activation or inflammation, metabolic reactions) that have the potential to disrupt developing organ systems but generally occur over a limited period of time that allows for recovery. Tolerable stress responses can be associated with significant trauma (eg, death of a loved one, a serious illness or injury, persistent family discord). Their essential characteristic is the availability of at least 1 supportive adult relationship that provides a sense of security, scaffolds the development of resilience, and helps restore physiologic homeostasis.

Toxic stress is characterized by strong, frequent, and/or prolonged activation of stress response systems, which can produce disruptions of brain circuitry and other biological systems and lead to health-damaging behaviors. When they occur during sensitive developmental periods, toxic stress responses can result in enduring structural changes and/or physiologic dysregulations that lead to lifelong problems in physical and mental health as well as in learning and behavior.⁵ In contrast to the mitigating impact of a supportive relationship that can make significant trauma tolerable, a toxic stress response is typically seen when protective relationships are not available or when the important relationship itself is the source of threat.

Reciprocal interactions between multisystem physiology and behavior are also the basis of the related concepts of allostasis and allostatic load and overload, first introduced more than two decades ago.¹⁴ Scientific advances now suggest an extension of that concept (which was centered originally on cardiometabolic reactions to stress and restoration of homeostasis) to include a wider set of systemic responses to a broader range of multiple organ-system challenges (eg,

chronic inflammation, insulin resistance) that can become increasingly difficult to change the longer and more persistent the insult.^{14,15} In addition to their biological impacts, behavioral responses are also important moderators of allostatic load and overload and multiorgan remodeling.¹⁴ As noted earlier, the source, type, or number of adverse experiences does not define toxic stress or allostatic load and overload; it is the magnitude, duration, and timing of the biological and behavioral disruptions that lead to increased risk of chronic illness later in life.

The continuous interplay among environmental and genetic factors is remarkably complex, and health outcomes are influenced robustly by their interactive effects. Childhood asthma provides an illustrative example. Although the causal interactions remain to be elucidated more precisely, exposure to pollutants, patterns of microbial colonization, metabolic impairment, and psychosocial stress during sensitive periods in development can all predispose to inflammatory airway responses to viruses, allergens, and other external stimuli in genetically susceptible children.^{16,17} Recurrent inflammation, in turn, triggers remodeling in airways, including altered autonomic responses and anatomic changes in the bronchial mucosa. Over time, these highly interactive processes can lead to bronchial hyperresponsiveness and irreversible airway narrowing, which (in the most severe circumstances) can predispose to chronic obstructive pulmonary disease and increased mortality.¹⁸

Learning how to adapt to a wide variety of challenges, from normative experiences to severe trauma and from specific environmental pollutants to ubiquitous microorganisms, is essential for healthy development. When access to

essential resources and supportive relationships is secure, the building blocks of resilience are strengthened. When adversity is extreme and protective relationships are not available (or when the burdens of structural inequities related to poverty or systemic racism are beyond the ability of families to control), multiorgan functional and structural remodeling can alter major regulatory processes, such as systemic inflammation and insulin responsiveness.^{16,19-21} In the final analysis, both the nature and the consequences of early-life challenges are influenced by variation in the sensitivity of different biological systems (eg, neural, metabolic, and immune) to physiologic perturbations at different ages, as well as by individual differences in sensitivity to context, all of which are determined by the interactive effects of genes, experiences, and developmental timing.⁵

CHALLENGES AND OPPORTUNITIES FOR CLINICAL PRACTICE AND ADVOCACY IN THE EARLY CHILDHOOD ECOSYSTEM

The rapidly moving frontiers of the biological sciences are transforming tertiary medical care (ie, precision medicine) and producing breakthrough outcomes in treating disease (eg, acute lymphoblastic leukemia and cystic fibrosis). Yet this knowledge is not being leveraged effectively to inform more effective strategies for promoting health and preventing illness.²² This discrepancy is particularly consequential in the early childhood period, when developing biological systems are most sensitive to environmental influences.

The role of pediatrics within the multisectoral context of early childhood policies and programs has been a topic of spirited debate for decades, yet the gaps between unmet needs and the realities of day-to-day practice have remained difficult to reduce.²³⁻²⁸ Efforts to improve

developmental screening and referrals to appropriate services continue to be particularly challenging to implement.²⁹ With current early childhood policies focused predominantly on school readiness, academic achievement, and later economic productivity, a strong case is emerging that science-informed investments in young children and their families could generate even larger returns to society by reducing the social and financial costs of preventable disease.³⁰ This growing understanding of the common foundations of health, learning, and behavior underscores 3 compelling opportunities for pediatric practice.

Opportunity 1: The Need to Expand the Toolbox of Effective Strategies for Strengthening the Foundations of Healthy Development in the Face of Adversity

Two recent AAP-sponsored projects illustrate the power of pediatric research, practice, and advocacy to produce significant impacts on child health and well-being as well as the compelling work that remains to be done. The first project identified “seven great achievements”³¹ in pediatric research over the past 4 decades, 3 of which (life-saving immunizations, reductions in sudden infant death syndrome associated with the Back to Sleep campaign, and decreased injuries and fatalities associated with car seats³¹) constitute a robust early childhood platform on which to build. A subsequent project was charged with predicting “the next 7 great achievements,”³² and 3 of the areas identified as ripe for breakthroughs (fetal and childhood antecedents of adult health and disease, the interaction of biology and the physical and social environment to promote health, and implementation and dissemination research to reduce global poverty³²) affirmed the potential power of science-based

innovation to mitigate the impacts of early adversity on lifelong health.

Two reviews of almost 4 decades of evaluation research on primary care interventions in the first 3 years after birth provide an important baseline for current pediatric practice and point to the need for more effective strategies. In the first article, the authors reviewed 47 publications from 1979 to 1999 that assessed developmental screening, parenting education, and anticipatory guidance but provided limited data on child outcomes.³³ In a more recent article, the authors reviewed 48 studies of 24 interventions published from 1999 to 2017 and found 20 positive outcomes related to parent behaviors and psychological well-being but only 6 impacts on child behavior; 4 reports of improved cognitive scores, 2 reductions in developmental delays, and no measures of child health. Attempts to compare findings across interventions in the latter review were constrained because of each study using a different child outcome measure, and the heterogeneity of results limited the ability to differentiate effective from noneffective practices.³⁴

Opportunity 2: Compelling Need to Revisit the Criteria Used to Designate an Intervention as Evidence Based and to Strengthen Measurement Capacity in the Early Childhood Period

Federal guidelines from the US Department of Education stipulate that the minimal requirements for evidence-based designation include a statistically significant difference between a treatment and comparison group on any child (or other relevant) outcome based on at least one study, without a requirement for replication.³⁵ In practice, when interventions designed to enhance child development are not linked to specific impacts on the basis of explicit theories of change, the variability of effects on multiple outcomes at different points in time is

nearly impossible to interpret and rarely reproduced. Focusing primarily on mean effects further obscures what may be working exceptionally well for some and poorly or not at all for others, which could inform a more targeted, layered, or proportionate approach to scaling.³⁶ Finally, preferential attention to statistical significance over magnitude of impact has contributed to remarkable complacency about the flat trajectory of average effect sizes for center-based early care and education programs for more than half a century.³⁷

Beyond the requirement for a new definition of evidence-based interventions, the need for more robust measurement capacity in the early childhood period is also clear. Assessments of development in primary health care are highly variable and typically limited²⁹ and rely largely on parent checklists of child skills and behaviors. Although the data generated by parent reports are subjective in nature and may be viewed with some degree of skepticism, these tools do provide valuable information about how primary caregivers view their child’s development, the influence of sociocultural factors and recent life experiences, and what respondents may feel comfortable sharing with professionals. That said, the complementary value of direct measures of child development and health (including indicators of stress activation and resilience) that could be administered during an office visit would augment the capacity of a primary care practice to (1) screen more effectively for individual differences in sensitivity to adversity; (2) make targeted referrals to well-matched services (when indicated), as well as convey credible reassurance for parents of children who are doing well; and (3) measure variation in short-term intervention effects to inform ongoing individualized management and

secure sustainable payment for effective services.

Opportunity 3: The Potential Benefits of 2 Complementary Pathways Toward Greater Impact on the Health and Development of Young Children and Families Facing Adversity

The first roadmap is familiar and predictable. It calls for increased funding for evidence-based programs, improved screening and referral for services, and stronger advocacy for attention to the social determinants of health, including poverty, racism, food insecurity, and unstable housing. The familiarity of this approach makes it easier to adopt, but its persistent inability to produce significantly larger impacts at scale underscores the need for additional strategies to augment its effectiveness.

The second pathway evokes instant recognition in the world of biomedical research. It is the road of dissatisfaction with small effects and the relentless pursuit of breakthrough impacts. It investigates causal mechanisms, generates science-based hypotheses to inform layered or new interventions, and measures predefined outcomes linked to specified theories of change. It is the road of iteration and learning from failure. Like the frontiers of precision medicine, it asks less about whether a treatment works and increasingly about for whom it works, why, and in what context. Learning from dramatic gains in the treatment of acute lymphoblastic leukemia, it is a road that has achieved breakthrough impacts by applying science-informed risk stratification to match different treatment protocols to identified subgroups.³⁸

Stated simply, 21st-century biology confirms what every parent knows: children do not all respond alike, either to hardships or to interventions. When provided through trusted relationships, pediatric primary care offers

a powerful delivery channel for individualized approaches to mitigating the consequences of early adversity and facilitating the development of resilience. Grounded in a prevention mindset, it provides early access to the largest number of children in a near-universal context at a time when both threatening and protective influences can have substantial impacts on the foundations of physical and mental well-being. Advances in science are fundamentally changing the way we understand, measure, and can potentially prevent adverse effects on early-childhood development and lifelong health.⁵ No other discipline or service delivery system is better positioned than pediatrics to leverage this rapidly moving knowledge base to achieve greater impact at scale.

CREATING A SCIENCE-BASED FRAMEWORK FOR 21ST-CENTURY PRIMARY CARE

The early childhood field needs to build a robust innovation platform driven by cutting-edge science, on-the-ground experience, entrepreneurial spirit, rigorous metrics, and a responsive mindset focused on clearly defined needs identified by families, service providers, community leaders, and public systems. Promising new strategies will be required at both the individual program level and the system level to achieve greater impact on the early roots of disparities in lifelong health. Primary care pediatrics should be the science engine driving this agenda.

Practice-Level Change

Pediatricians must lead the quest for more effective interventions to protect developing biological systems from the disruptive effects of excessive adversity beyond providing information on child development for parents and enriched learning experiences for young children. With that objective in mind, the biology of

adversity and resilience points to 3 guiding principles that can inform both improvement of existing practices and the design and testing of new strategies³⁹:

1. Support responsive relationships: Individualized “serve and return” interactions between young children and the adults who care for them strengthen developing brain architecture and other biological systems and facilitate the development of adaptive responses to adversity.⁴⁰ When caregivers have difficulties interacting with their children, relationship-focused coaching can make an important difference. A recently updated AAP policy statement on preventing childhood toxic stress⁴¹ underscores the central importance of promoting “safe, stable, and nurturing relationships” in the context of pediatric primary care, as exemplified in previous AAP reports on managing perinatal depression,⁴² fostering male caregiver engagement,⁴³ partnering with home visiting programs,⁴⁴ encouraging developmentally appropriate play,^{45,46} discouraging screen time,⁴⁷ and promoting shared book reading.⁴⁸
2. Reduce sources of stress: Interventions that lessen economic, psychosocial, and health burdens on families, many of which are associated with structural inequities that are beyond the capacity of pediatricians to address directly, increase adult bandwidth for providing positive caregiving. Financial supports to help meet basic needs (eg, rent, food, diapers) and interventions that reduce more proximal stressors on neurobiological, immune, and metabolic systems (eg, poor nutrition, environmental toxicants, chronic microbial exposures) all contribute to promoting the

healthy development of young children. An AAP policy statement on poverty and child health provides an overview of how family-centered medical homes can reduce stresses on families facing financial instability through linkages to resources and coordination of needed services with community partners.⁴⁹

3. Strengthen core skills to provide a well-regulated caregiving environment: The development of the brain and other biological systems is facilitated by regularized daily routines (eg, mealtime, sleep time, play) scaffolded by caregivers with the skills needed to provide an environment of stability and predictability. The capacities of parents and other primary caregivers to set and meet goals and manage their own behavior and emotions can be strengthened through coaching and practice.⁵⁰ Integrated behavioral health services offer a variety of models and strategies for providing such interventions within the context of primary care.^{51,52}

Growing interest in biological measures of stress activation and adaptation (eg, cortisol, proinflammatory cytokines, metabolic biomarkers) in young children presents promising potential for pediatric practice,⁵ but their beneficial implementation will require both rigorous scientific validation and thoughtful preparation.

- From a scientific perspective, normative values for young children at different ages must be established, and 3 key questions must be addressed: (1) Does the measure reflect current biological function? (2) Does the measure help identify children who are and are not exhibiting greater susceptibility to adversity? and (3) Can the measure be used to quantify intervention effects?
- From a preparation perspective, critical prerequisites to ethical and effective implementation include the following: (1) investigation of feasibility, acceptability, and affordability in a diversity of practice settings; (2) increased public understanding of the effects of early adversity on child well-being and lifelong health; and (3) informed professional and parent engagement to ensure appropriate interpretation by clinicians and full understanding by parents or other caregivers that measures of excessive stress activation in young children are indicators of relative risk, not predictors of specific diseases or developmental impairments. When validated scientifically, such measures could strengthen the doctor-family relationship if implemented in ways that empower parents or other primary caregivers, protect autonomy and confidentiality, and prevent inappropriate labeling or unintended consequences. These latter concerns are critically important for children and families of color given the extensive history of egregious misuse of biology to advance racist ideologies and exploitation of marginalized groups for research purposes.

Population-Level Change

Beyond the individual achievements of model practices, greater impact at scale on the lives of young children facing adversity will require substantial modifications in pediatric training, practice, impact evaluation, and payment systems.

- Significantly more attention to the biology of adversity and resilience in medical school and residency training programs and increased attention to the deeply embedded influence of racism on the delivery of health care services are needed to equip researchers, clinicians, and advocates with the knowledge needed to play a leadership role in

developing, iterating, and implementing science-based practice models that produce better outcomes for all children.

- Brief clinical interactions and high patient volume undermine the ability of pediatricians to build the trusted relationships needed to support families experiencing challenges. Stronger evidence (ie, more robust measures of impacts) of effective practices that require more time to deliver will strengthen the case for payment for longer visits, and expertise in value-based reimbursement policies will be needed to secure its sustainability.
- Intervention impacts on parents and reductions in health care use (eg, emergency department visits and hospitalizations) are clearly important, but they are not a sufficient proxy for well-documented direct effects on child health or development.
- Cross-sector coordination of community-based services is an important objective, but improved collaboration alone will not produce positive child outcomes if the component services have limited impacts.

Greater attention to social determinants of health is essential, but the identification of increased risk must be followed by the implementation of effective strategies that produce measurable effects.

- AAP policy statements on poverty⁴⁹ and racism⁵³ provide a powerful platform for vigorous advocacy. Achieving population-level impact will depend on leveraging the influence of that platform through strategic collaborations with carefully selected partners who have the complementary power and expertise needed to confront the upstream effects of poverty, systemic racism, and violence at a macro level.^{8,54,55}

- Measuring demographic risk factors or adverse childhood experiences (eg, by calculated adverse childhood experience scores) at a population level can provide valuable data for policy makers, but the identification of individual risk and allocation of resources would be enhanced substantially by direct measures of child health and development within the context of primary health care to determine priorities for intervention and match specific services to identified needs.

CONCLUDING THOUGHTS

The rapidly moving frontiers of 21st-century science are providing unparalleled opportunities to develop a deeper understanding of healthy development broadly and, more specifically, a more integrated, whole-child approach to the biology of adversity and resilience. Building on growing public awareness of the impact of early experiences on the developing brain, pediatricians are well positioned to drive an expanded understanding of how the brain is connected to the rest of the body and how the interactive influences of genetic predispositions, physical and social environments, and developmental timing affect the foundations of both school readiness and lifelong health.

At the practice level, current state of the art must be viewed as a starting point, not a destination. Increasing evidence of the importance of the

prenatal period and early infancy for the developing brain, the immune system, and metabolic regulation underscores 2 critical roles for pediatric primary care in an early childhood policy environment that is currently focused largely on preschool for ages 3 and 4. The first is the importance of substantially enhanced connection to prenatal services. The second is the compelling need for more effective strategies to address adversity in the first 2 to 3 years after birth, when a variety of interventions have been shown to produce varied benefits, short-term gains have been difficult to replicate, and impact at scale remains elusive. Advances in science suggest that these latter challenges are related to limitations in measurement capacity and a disproportionate focus on the average effects of existing programs that have constrained the field's capacity to learn from variation in sensitivity to environmental influences and differential responses to specific interventions. Impact evaluation must move beyond general questions about whether a specific intervention works to more focused inquiries about what works for some children and in what contexts (which should trigger targeted scaling) and what is not working for others (which should catalyze the design and testing of alternative approaches).

At a population level, new strategies are needed to confront the hardships and threats that intergenerational poverty, systemic racism, and other

deeply embedded structural inequities impose on families raising young children. Although the capacity of clinical services alone to address these complex societal problems is limited, a strong pediatric voice within strategically selected partnerships can add powerful impact.

Every program, sector, and policy that affects the lives of young children and their families, as well as expectant mothers and fathers before and during pregnancy, presents opportunities to build resilience and protect developing biological systems from the disruptive effects of excessive adversity. The pediatric community can play a critical role by bringing science-informed thinking and testable hypotheses to the quest for greater impact at scale. The opportunity for pediatricians to serve as the leading edge of science-based innovation across the early childhood ecosystem has never been more compelling.

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ABBREVIATION

AAP: American Academy of Pediatrics

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