Exposures to adverse environments, both psychosocial and physicochemical, are prevalent and consequential across a broad range of childhood populations. Such adversity, especially early in life, conveys measurable risk to learning and behavior and to the foundations of both mental and physical health. Using an interactive gene-environment-time (GET) framework, we survey the independent and interactive roles of genetic variation, environmental context, and developmental timing in light of advances in the biology of adversity and resilience, as well as new discoveries in biomedical research. Drawing on this rich evidence base, we identify 4 core concepts that provide a powerful catalyst for fresh thinking about primary health care for young children: (1) all biological systems are inextricably integrated, continuously “reading” and adapting to the environment and “talking back” to the brain and each other through highly regulated channels of cross-system communication; (2) adverse environmental exposures induce alterations in developmental trajectories that can lead to persistent disruptions of organ function and structure; (3) children vary in their sensitivity to context, and this variation is influenced by interactions among genetic factors, family and community environments, and developmental timing; and (4) critical or sensitive periods provide unmatched windows of opportunity for both positive and negative influences on multiple biological systems. These rapidly moving frontiers of investigation provide a powerful framework for new, science-informed thinking about health promotion and disease prevention in the early childhood period.

Differential child health outcomes are shaped by developmental contexts through ongoing, interactive adaptations that begin at conception and continue throughout life. Although biological effects of both physical and social adversities on the brain have received the most attention in the world of early childhood policy and programs, it is clear that the mediators and moderators of challenging exposures extend well beyond neural circuitry, and researchers are documenting increasing evidence of the extraordinary importance of the prenatal period and early infancy for the developing immune system and metabolic regulation. In this article, together with its companion article, we provide clinicians and researchers with a synopsis of advances in developmental biomedical research and their implications for pediatric practice.

Research on health and disease in children has traditionally assessed the roles of genetic and environmental factors separately on the basis of the implicit assumption that each category can be investigated independently, irrespective of the other’s influences. Moreover, the existence of specific, temporal windows of opportunity during which environmental factors...
can prevent or increase the risk for impairment is increasingly acknowledged but seldom addressed empirically. The convergence of multiple domains of developmental biomedical research of the interactive effects of genetic and environmental factors on health trajectories for different organs, at different points in time, is dramatically changing our ability to understand the childhood origins of lifelong disease and well-being. These investigations provide a compelling framework for a new era in science-based pediatric practice informed by the following advances:

- a deeper understanding of how multiple genes influence susceptibility and resilience, how genes and environmental conditions interact, and how epigenetic and metabolic processes affect the outcomes of adversity exposures;
- fresh awareness of how developmental time, as a third critical variable, can moderate the health effects of toxic stress in interaction with genetic and environmental variation;
- new knowledge of the sources and consequences of individual differences in children’s sensitivity to adversities in their families and communities;
- greater appreciation for how all biological systems respond to adversity in an integrated way, by operating together in networks, at multiple levels of biological complexity;
- a heightened awareness of how stressors in the psychosocial and physical environment co-occur, especially within disadvantaged populations; and
- the powerful role of environmental protective factors, their potential for building more effective prevention strategies, and the need for a balanced approach to studying both resilience and risk.

Figure 1 provides a conceptual map of this new developmental biology of adversity. This image illustrates triadic relations among genes, environments, and developmental time and their interactive roles in the foundations of health and the pathogenesis of impairments. Together, these roles describe an interactive GET framework, in which genetic differences, environmental exposures, and developmental timing act synergistically and contingently. Genetic variation that determines risk is often conditioned on environmental factors that interactively regulate gene expression through epigenetic processes.

Both toxic and protective aspects of children’s environmental experiences, at the levels of family and community, exert gene transcription-modifying influences on risks for ill health and maladaptive behavior. Exposures to psychosocial stressors, such as adverse childhood experiences (ACEs) or the structural inequities of systemic racism, and physicochemical toxins, such as pollutants or excessive noise, often share common grounding in a scarcity of essential resources. On the other hand, supportive environments that buffer the effects of adversity typically include access to sufficient material assets and protective caregiving. Lastly, the temporal dimension of these 3-way interactions may include experience-dependent critical or sensitive periods, during which multiple developing systems are fine-tuned physiologically. Developmental plasticity and malleability are highest during these periods, but critical periods have more sharply defined beginning and end points and plasticity that is not graded over time, whereas sensitive periods have less well-defined onsets and endings, with an extended plasticity gradient.

Under pathogenic conditions, GET interactions can give rise to disorders of physical and/or mental health or to intermediate phenotypes, such as emotion dysregulation, disturbed adrenocortical reactivity, inflammation, or metabolic dysfunction. The causal pathways linking these heightened risks for disorders of health can be mediated or influenced by factors that hasten or temporize, as well as intensify or restrain, the emergence of pathology. These include differential susceptibility to environmental conditions, immune competence, the regulation of metabolic and inflammatory processes, and the microbiomes.

It is important to underscore that the same interactions that create conditions for disorders at one end of the spectrum can strengthen the foundations of resilience at the other end. Health is not simply an avoidance of disease but a result of key protective influences during critical or sensitive developmental stages, which can enhance expression of protective genetic elements. Importantly, the frontiers of evidence in GET domains have come to bridge the boundaries among them as their influences have been increasingly revealed as fundamentally interactive.

**GENES**

British epidemiologist Geoffrey Rose observed that the most difficult disease risk factors to detect are, ironically, those that are most prevalent. For example, ubiquitous smoking in a hypothetical population would make smoking the hardest environmental risk factor to identify in the subgroup that developed lung cancer. Something similar has been at work in our recognition of toxic stress as a key etiologic factor for childhood disorders and persistent disparities in population health. Extensive evidence indicates that early adversities, including child maltreatment, family or community violence, parental substance abuse or mental disorders, and the burdens of poverty or racism,
are highly prevalent, affecting at least half of children by the time they reach adolescence.\textsuperscript{16,17} Moreover, one-half of those who sustain such exposures exhibit some form of developmental psychopathology, and at least one-third of adult mental health disorders are attributable to ACEs.\textsuperscript{18}

The hardships and threats associated with systemic racism, personally experienced discrimination, and other forms of institutionalized marginalization are particularly virulent and pervasive influences on child health,\textsuperscript{19} and they are based entirely on socially constructed categories rather than any intrinsic genetic partitioning of human populations.\textsuperscript{20,21} Moreover, children experiencing the burdens of structural inequities are not only disproportionately exposed to psychosocial stressors, but also to physicochemical toxicants such as lead and pesticides.\textsuperscript{22,23} Extensive biomedical research has been frequently blinded to these converging adversity effects by both their extraordinary prevalence in human lives and by a resistance to acknowledge psychosocial influences on biological health end points.

That said, increasing research is now revealing that the health consequences of both psychosocial stressors and environmental toxicants are often conditioned by genetic variation with respect to individual susceptibility to adversity.\textsuperscript{24} The risk of developing adult psychopathology, for example, is related to an interaction between childhood trauma and a functional polymorphism in the \textit{FKBP5} gene that controls aspects of glucocorticoid responses to stress.\textsuperscript{25} Similarly, the neurodevelopmental effects of lead exposure are amplified by the...
presence of a sensitizing polymorphism in the gene coding for δ-aminolevulinate dehydratase, an enzyme in the heme synthesis pathway. Thus, although the independent biological effects of environmental factors and genetic variation can each be substantial, gene-environment interactions (GxEs) also have large effect sizes and appear to be far more prevalent than initially thought. For pediatricians, a new understanding of how individual genetic variation can play a role in the health consequences of significant environmental trauma and threats is central to advancing the practice of medicine.

This interplay between genes and environments takes at least 3 forms, as summarized in Table 1. First, gene-environment correlation (rGE) arises when individuals with certain genetic variants choose, alter, or create the social or physical environments in which they live. An adolescent with a genetic predisposition to antisocial behavior, for example, may actively seek risk-taking experiences, such as driving after drinking, or students with a particular genotype may gravitate to certain kinds of classroom activity while foregoing others. Here, genetic variation and environmental exposures are correlated but not causally interactive.

Second, there are instances in which genetic variations come into play only in the presence of specific environmental conditions (GxE) and, alternatively, some environmental influences become apparent only among individuals carrying a particular genetic variant. The level of endotoxin exposure early in life, for example, predicts atopic sensitization leading to asthma, but only among children with a specific variant of the CD14 gene coding for a pattern recognition receptor on cell surfaces. In other examples, ACEs are associated with later maternal insensitivity, but only among girls with a single nucleotide polymorphism in the PRKG1 gene, and children carrying the 7-repeat allele of the DRD4 gene have increased fat intake when reared in socioeconomically disadvantaged conditions.

Polymorphisms in the oxytocin and oxytocin receptor genes also predict measures of maternal-infant caregiving and maternal depression but are limited to women reporting to have themselves received poor quality early maternal care as children. A third form of gene-environment interplay includes biological processes in which environmental exposures regulate or calibrate the timing and level of expression of specific sets of genes, resulting in differences in behavior or disease risk. These epigenetic gene-regulatory processes (eGEs) can take a variety of forms, including the following: methylation or hydroxymethylation of cytosine dinucleotides (DNA regions in which cytosine nucleotides are followed by guanine nucleotides [CpG sites]) in DNA; posttranscriptional control of gene expression by small, noncoding RNAs; and posttranslational modifications of the histone proteins that DNA is wrapped around within chromatin. Methylation of CpG sites within promoter regions has generally repressive effects on gene transcription, whereas epigenetic marks within gene-coding regions are more often linked to an upregulation of transcription. These epigenetic modifications have short- and long-term effects on stress-responsive biological systems and work by changing the structure of the genome’s chromatin packaging. Such epigenetic processes have been implicated in the regulation of the hypothalamic-pituitary-adrenocortical axis and the autonomic nervous system and in the acquisition of health risks from early life adversities and trauma.

Each form of gene-environment interplay (rGE, GxE, and eGE) has been increasingly documented in relations among early childhood adversity, toxic stress, and disorders of health and development. Although doubts have sometimes arisen regarding the replicability of GxE interactions, recent meta-analyses have confirmed their key roles in pathogenesis. Other work has suggested that genetic variants and differences in gene expression may influence outcomes not just by increasing morbidity under conditions of adversity, but also by enhancing an individual child’s sensitivity to both positive and negative environmental conditions, a so-called differential susceptibility perspective. New research also suggests that a deeper understanding of gene-environment interplay may be advanced by employing polygenic risk scores that incorporate the

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contributions of many common genetic variants across the genome,\textsuperscript{5,41} or even an omnigenic array of both core and secondary genetic networks.\textsuperscript{51} Finally, when examined explicitly, developmental timing may play an important role as a moderator of GxE effects on health and disease.\textsuperscript{52}

**ENVIROMENTS**

The well-established connection between early environmental exposures to significant adversity and modifications of the developing brain has been bolstered by growing evidence that other organs are also affected and that these collective changes render a child more susceptible to “second or third hits” by physical or psychosocial stressors later in life.\textsuperscript{53-55} Stressors produce chemical mediators that trigger adaptive mechanisms in multiple organ systems, termed allostasis, with the goal of maintaining homeostatic balance. Continued exposure to adversity, however, can result in an allostatic load or overload condition, in which neural circuit and cardiometabolic changes have lasting costs in dysfunction and disease.\textsuperscript{56}

There is also increasing evidence from both animal and human studies that persistently elevated systemic inflammation can produce enduring molecular and structural remodeling of multiple organ systems, increasing the risk of later impairments in both physical and mental health.\textsuperscript{57}

Children experiencing the stressors of poverty, racism, unsupportive caregiving, and/or maltreatment have increased incidences of inflammation-related obesity and elevated blood pressure.\textsuperscript{58,59} Heightened cardiometabolic risk has also been documented in adolescents who grew up during the recession that followed the 2007–2008 financial crisis.\textsuperscript{50}

Unsupportive parenting in childhood can similarly lead to increased inflammatory reactivity to major life events,\textsuperscript{58} likely through sympathetic activation of inflammatory cytokine production. Increased inflammation is associated with insulin resistance, type 2 diabetes, increased BMI, and altered myelin structure in the developing brain.\textsuperscript{61,62} Over the life course, insulin resistance is associated with increased risk of a subtype of major depression as well as Alzheimer disease.\textsuperscript{63}

This pathogenic cascade of adversity-associated morbidities appears to begin with a chronic proinflammatory state. Major hardships or threats in the family environment, for example, are associated in childhood with upregulation of Nuclear Factor-κB-responsive genes in peripheral blood mononuclear cells, such as lymphocytes and monocytes,\textsuperscript{64} and this effect may persist into adulthood.\textsuperscript{65} Nuclear Factor-κB is a transcription factor that plays a role as master regulator in many critical responses to environmental stimuli, including cell survival, DNA transcription, and cytokine production during acute infection. Its dysregulation may result in chronic inflammation leading to multiorgan remodeling and a host of chronic illnesses.

These conclusions are supported by a comprehensive meta-analysis of >40 studies assessing associations between childhood trauma and peripheral levels of 3 key inflammatory markers in adults: C-reactive protein, interleukin 6 (IL-6), and tumor necrosis factor α.\textsuperscript{66} Findings revealed a significant association between early adversity and all biomarkers studied, with the largest effect sizes for tumor necrosis factor α, followed by IL-6 and C-reactive protein. A deeper understanding of these associations between childhood stressors and adult proinflammatory signaling could lead to more effective strategies for preventing many chronic conditions, including cardiovascular disease,\textsuperscript{60,67} viral hepatitis,\textsuperscript{68} liver cancer,\textsuperscript{69} asthma,\textsuperscript{70} chronic obstructive pulmonary disease,\textsuperscript{57} autoimmune diseases,\textsuperscript{71} poor dental health,\textsuperscript{72} and depression.\textsuperscript{73}

As noted earlier, among many possible mechanisms for the connection between childhood trauma and inflammatory phenotypes, epigenetic processes controlling gene expression are worthy of attention. Peripheral blood mononuclear cells in adults who were exposed to emotional neglect or violence in childhood exhibit increased IL-6 responses after exposure to social stress tests, especially in subjects who had diminished DNA methylation of the IL-6 gene promoter.\textsuperscript{74} These results suggest the future possibility that susceptibility to excessive, early adversity could be assessed by screening the epigenome to identify children most at risk for later disease. By using a proportionate universality strategy,\textsuperscript{75} in which interventions are attuned to children’s differential sensitivities and family resources, needs, and preferences, maximal efficacy of protective and therapeutic services may be achievable.

There is also mounting evidence implicating chronic, systemic inflammation in the composition of the microbiome in both the gut and airways. Recent studies also indicate that there are critical periods in infancy when disruptions of microbial colonization of mucosal tissues can lead to persistent defects in the development of specific T-cell subsets with lifelong impacts on physical health.\textsuperscript{76} In neonates, isolation of certain bacterial species from the upper airway or specific microbial populations in the gut is associated with the subsequent risk of asthma.\textsuperscript{77,78} Specific gut microbiome communities have also been reported in children who become overweight or obese.\textsuperscript{79} These findings are stimulating further examination of the intriguing hypothesis that alterations in the dynamic relation
between the immune system and mucosal microbes (the so-called microbial-mucosal unit) may occur early in life and predispose young children to greater risk for chronic inflammatory conditions.

Although there are currently no data on humans revealing a direct association between excessive, early adversity and the microbiome, a diverse set of animal models has shown that infant-maternal separation and other experimental models of early adversity may result in microbiome effects that persist into adulthood. These findings suggest a new causal pathway to chronic disease: excessive, early adversity leading to disruption of the microbial-mucosal unit. Chronic inflammation and subsequent illness are also associated with higher levels of family stress. This hypothesized cascade of biological disruptions in the child and emergent adversities within the family suggests scalable possibilities for prevention that begin with maintaining or restoring specific microbiota.

Finally, there is evidence that maternal warmth and responsive relationships in adolescence can buffer the adverse effects of chronic immune system activation. As one example, a family-based intervention provided for African-American youth who had grown up under early conditions of poverty produced reductions in inflammation, a decreased incidence of prediabetes, and the promotion of healthy brain development.

Preventive interventions to mitigate the effects of early adversity, combined with identifying highly susceptible children, offer the potential to prevent diseases that account for a large proportion of US annual health expenditures.

**TIME**

The basic concept of critical or sensitive periods in the development of brain circuitry refers to windows of plasticity during which identified regions are most sensitive to the effects of experience. Beyond this well-established cornerstone of neurobiology, specific temporal patterns of gene expression have been identified that provide the molecular ingredients (eg, structural and signaling proteins, transcription factors, receptors, and ion channels) for the development of the specialized cells in many other organs and systems. Over time, these cells build the capacity to respond to intrinsic cross-talk among systems (eg, gastrointestinal, immune, and neural) as well as to extrinsic information from prenatal (eg, maternal, placental, sensory) and postnatal (eg, nutritional, physical environment, social relationship, sensory) factors. The varying degrees to which different cells and organs respond to external influences define their sensitivity, and this typically occurs during specific periods in development that may overlap or vary by physiologic system.

These common principles described above operate across systems and at varying levels of biological complexity. Current understanding of the origins of peanut allergy provides one illustrative example of how timed exposures can influence sensitivity. Severe (and often life-threatening) allergic responses to ingested peanuts have increased significantly during the last decades, and the exact cause is still unknown. Until recently, the accepted strategy for preventing peanut allergy was to avoid ingestion early in life. In stark contrast, a recent clinical trial showed that systematic, oral administration of peanuts to high-risk infants who were not already sensitized markedly reduced the incidence of subsequent allergy. These results indicate that the response to the peanut allergen is dependent on timing and amount, with exposure being either tolerated or sensitizing depending on whether it occurs before or after the selection of specific cells that mediate the allergic response.

Perhaps the most familiar examples of differential plasticity over time come from extensive brain research demonstrating that some neural circuits respond within months to experiences promoting maturation of function (eg, sensory processing), whereas other circuits remain sensitive to external influences for decades (eg, executive functioning). At the end of the 20th century, neuroscientists characterized the critical or sensitive period for a particular sensory function (including its onset, peak, and reduced sensitivity to experience, which together drive changes in circuit organization and function), irrespective of whether the circuit was on a normal trajectory (eg, in binocular visual acuity) or disrupted developmentally (eg, in amblyopia). Within that framework, changes induced by experiences during the critical or sensitive period can occur at the structural (ie, wiring diagram), molecular (ie, epigenome), and physiologic (ie, cell signaling) levels.

Recent breakthrough research has revealed that the gut microbiome (in both human infants and animal models) exhibits the same critical or sensitive period effect because the infant gut microbiome is established through maternal transmission and early environmental seeding. There is also evidence that microbial colonization influences lifelong immune function, either directly through immune modulation or indirectly through metabolites generated by gut bacteria. These influences have been documented for respiratory, gastrointestinal, and brain functions.

The developmental mechanisms that establish the gut microbiome and can result in increased health risks are
a rich area of current clinical and basic research. Evidence for critical or sensitive period development in other peripheral systems in humans is more limited. Given highly conserved biological adaptation and plasticity to environmental cues (from insects to humans), \(^\text{96}\) it is likely that, in the next decade, breakthrough discoveries in this domain of investigation will be realized.

Although issues related to critical and sensitive periods in brain development used to be considered relevant primarily for sensory systems, research now reveals that neural circuits involved in emotional regulation and cognition are also sensitive to the timing of experiences, and these periods determine relative responsiveness to stressors. For example, the Bucharest Early Intervention Project randomly assigned infants and toddlers living in orphanages into foster care homes at different times, largely after 12 months of age. \(^\text{100}\) The unavoidable differences in placement timing were dependent on the limited availability of foster care families, which created a natural experiment to investigate the impact of enriched environments at different ages. Extensive follow-up data demonstrated significantly better outcomes in cognitive (eg, language, IQ) and emotion regulatory functions (eg, stress responsiveness, attachment, stereotypes) for children who received foster care placements, with the best outcomes for those placed at younger ages (particularly before 2 years). \(^\text{3}\) These findings illustrate 2 core features of neuroplasticity\(^\text{5,101}\): (1) although the identification of specific circuits is continuing to emerge, cognitive and socioemotional functions appear to exhibit critical or sensitive periods of development and adaptation; and (2) timing varies across functions.

Different neural circuits and the functions they mediate exhibit varied responsiveness to experiences depending on timing, and differences in timing for specific experiences can result in different functional outcomes. For example, during the first 10 days after birth, a rodent pup exposed to a negative stimulus paired with maternal odor will paradoxically exhibit enhanced attraction to that odor. In contrast, when elicited after day 10, the same procedure results in the expected, conditioned aversion to maternal odor, except in the mother’s presence. \(^\text{102}\)

As the complexity of developmental plasticity has become increasingly apparent over the past decade, 2 discoveries have generated a clearer understanding of the opening and closing of critical or sensitive periods in the cerebral cortex. The first is the identification of molecular and cellular accelerators and brakes that regulate onset, duration, and cessation. \(^\text{103,104}\) This led to the discovery that the balance between neuronal excitation and inhibition is highly conserved, including in humans. This balance is essential for the ability to process complex information and has been shown to be disrupted in certain mental illnesses. \(^\text{105}\) Subsequent investigations have defined the excitatory and inhibitory neuronal cell types responsible for setting parameters that mediate plasticity through their own pace of maturation. Research has even identified the specific type of inhibitory neurons for which changes in the timing of maturation influence experiential effects on connections during critical or sensitive periods. Both genetic and environmental factors control the expression of specific molecules during development that can accelerate, keep open, or halt such periods. \(^\text{106–108}\)

Implicit in these discoveries is the future potential for targeted manipulation of critical period timing to optimize the impact of preventive interventions.

Another breakthrough discovery is the recognition that specific experiences occurring well past the end of a critical or sensitive period can still change functional outcomes, although at a higher physiologic cost. This finding comes from both animal and human research in which the balance between excitatory and inhibitory influences was manipulated in various ways (eg, by environmental stress, physical exercise, disrupted cellular metabolism, and genetic or pharmacologic manipulation of $\gamma$-aminobutyric acid neurotransmission) to demonstrate that the duration, and even the reopening, of critical periods is malleable. \(^\text{109}\) Examples of this phenomenon are the ability to teach perfect pitch to human adults, \(^\text{110}\) the restoration of binocular vision in animal models after critical period closure, \(^\text{111}\) and the extension of treatment age range for human amblyopia. \(^\text{112}\) Recent research on correcting gut microbiome balance past the infancy period, in which healthy patterns are generally established, represents another frontier of investigation for which new discoveries are on the horizon. \(^\text{113}\)

Current research on plasticity during critical or sensitive periods is challenging long-standing principles related to health promotion and disease prevention. There is growing evidence that factors affecting critical or sensitive period timing can modify onset, duration, and closure. The discovery that significant adversity can accelerate the opening and closure of critical periods for the maturation of fear circuitry in animal models has compelling implications for early intervention in humans. \(^\text{114}\) The recognition that critical period timing is likely to vary among children presents both a challenge and an opportunity for developing preventive interventions in the early childhood years and for assessing their effectiveness at different ages. \(^\text{87}\)

Finally, a deeper understanding of
developmental biology is pointing to the need for fresh thinking about the importance of critical or sensitive periods for all developing organs and biological systems, not just the brain.

CONCLUDING THOUGHTS
Advances in our understanding of how genes, environments, and developmental timing interact dynamically provide a compelling opportunity for leveraging 21st-century science to inform new approaches to health promotion and disease prevention in the context of pediatric practice. One of the most salient discoveries over recent decades is the integrated nature of the developmental process across biological systems. Equally important, pathologic processes for a range of disorders begin early, even prenatally, and many exert their most potent and long-lasting effects in the first few years after birth. Genetic variation plays a powerful role in susceptibility to specific morbidities, but its consequences are frequently altered by environmental and temporal effects on gene transcription. In a complementary fashion, the strong impacts of both toxic and health-promoting environments on child well-being can be either augmented or blunted by genome-derived susceptibility or the developmental timing of the exposures. The provision of responsive caregiving environments that are attuned to the varied assets and needs of young children, the targeting of specific prevention strategies or treatments on the basis of differential susceptibility, and the timing of interventions to coincide with critical or sensitive periods of optimal receptivity are all examples of how the future of pediatric practice must be guided by a deeper understanding of the mutual, interactive influences of genes, environments, and time.

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ABBREVIATIONS
ACE: adverse childhood experience
eGE: epigenetic gene-regulatory process
GET: gene-environment-time
GxE: gene-environment interaction
IL-6: interleukin 6
rGGE: gene-environment correlation

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