PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The Lifelong Effects of Early Childhood Adversity and Toxic Stress

Jack P. Shonkoff, Andrew S. Garner, THE COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, COMMITTEE ON EARLY CHILDHOOD, ADOPTION, AND DEPENDENT CARE, AND SECTION ON DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS, Benjamin S. Siegel, Mary I. Dobbins, Marian F. Earls, Andrew S. Garner, Laura McGuinn, John Pascoe and David L. Wood

Pediatrics 2012;129;e232; originally published online December 26, 2011;
DOI: 10.1542/peds.2011-2663

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

TECHNICAL REPORT

The Lifelong Effects of Early Childhood Adversity and Toxic Stress

abstract

FREE

Advances in fields of inquiry as diverse as neuroscience, molecular biology, genomics, developmental psychology, epidemiology, sociology, and economics are catalyzing an important paradigm shift in our understanding of health and disease across the lifespan. This converging, multidisciplinary science of human development has profound implications for our ability to enhance the life prospects of children and to strengthen the social and economic fabric of society. Drawing on these multiple streams of investigation, this report presents an ecobiodevelopmental framework that illustrates how early experiences and environmental influences can leave a lasting signature on the genetic predispositions that affect emerging brain architecture and long-term health. The report also examines extensive evidence of the disruptive impacts of toxic stress, offering intriguing insights into causal mechanisms that link early adversity to later impairments in learning, behavior, and both physical and mental well-being. The implications of this framework for the practice of medicine, in general, and pediatrics, specifically, are potentially transformational. They suggest that many adult diseases should be viewed as developmental disorders that begin early in life and that persistent health disparities associated with poverty, discrimination, or maltreatment could be reduced by the alleviation of toxic stress in childhood. An ecobiodevelopmental framework also underscores the need for new thinking about the focus and boundaries of pediatric practice. It calls for pediatricians to serve as both front-line guardians of healthy child development and strategically positioned, community leaders to inform new science-based strategies that build strong foundations for educational achievement, economic productivity, responsible citizenship, and lifelong health. *Pediatrics* 2012;129:e232–e246

INTRODUCTION

Of a good beginning cometh a good end.

John Heywood, *Proverbs* (1546)

The United States, like all nations of the world, is facing a number of social and economic challenges that must be met to secure a promising future. Central to this task is the need to produce a well-educated and healthy adult population that is sufficiently skilled to participate effectively in a global economy and to become responsible stakeholders in a productive society. As concerns continue to grow about the quality of public education and its capacity to prepare the nation's future workforce, increasing investments are being made in

Jack P. Shonkoff, MD, Andrew S. Garner, MD, PhD, and THE COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, COMMITTEE ON EARLY CHILDHOOD, ADOPTION, AND DEPENDENT CARE, AND SECTION ON DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

KEY WORDS

ecobiodevelopmental framework, new morbidity, toxic stress, social inequalities, health disparities, health promotion, disease prevention, advocacy, brain development, human capital development, pediatric basic science

ABBREVIATIONS

ACE—adverse childhood experiences
CRH—corticotropin-releasing hormone
EBD—ecobiodevelopmental
PFC—prefrontal cortex

www.pediatrics.org/cgi/doi/10.1542/peds.2011-2663

doi:10.1542/peds.2011-2663

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

the preschool years to promote the foundations of learning. Although debates about early childhood policy focus almost entirely on educational objectives, science indicates that sound investments in interventions that reduce adversity are also likely to strengthen the foundations of physical and mental health, which would generate even larger returns to all of society.[1,2] This growing scientific understanding about the common roots of health, learning, and behavior in the early years of life presents a potentially transformational opportunity for the future of pediatrics.

Identifying the origins of adult disease and addressing them early in life are critical steps toward changing our current health care system from a "sick-care" to a "well-care" model.[3–5] Although new discoveries in basic science, clinical subspecialties, and high-technology medical interventions continue to advance our capacity to treat patients who are ill, there is growing appreciation that a successful well-care system must expand its scope beyond the traditional realm of individualized, clinical practice to address the complex social, economic, cultural, environmental, and developmental influences that lead to population-based health disparities and unsustainable medical care expenditures.[2,6,7] The science of early childhood development has much to offer in the realization of this vision, and the well-being of young children and their families is emerging as a promising focus for creative investment.

The history of pediatrics conveys a rich narrative of empirical investigation and pragmatic problem solving. Its emergence as a specialized domain of clinical medicine in the late 19th century was dominated by concerns about nutrition, infectious disease, and premature death. In the middle of the 20th century, as effective vaccines, antibiotics, hygiene, and other public health measures confronted the infectious etiologies of childhood illness, a variety of developmental, behavioral, and family difficulties became known as the "new morbidities."[8] By the end of the century, mood disorders, parental substance abuse, and exposure to violence, among other conditions, began to receive increasing attention in the pediatric clinical setting and became known as the "newer morbidities."[9] Most recently, increasingly complex mental health concerns; the adverse effects of television viewing; the influence of new technologies; epidemic increases in obesity; and persistent economic, racial, and ethnic disparities in health status have been called the "millennial morbidities."[10]

Advances in the biological, developmental, and social sciences now offer tools to write the next important chapter. The overlapping and synergistic characteristics of the most prevalent conditions and threats to child well-being—combined with the remarkable pace of new discoveries in developmental neuroscience, genomics, and the behavioral and social sciences—present an opportunity to confront a number of important questions with fresh information and a new perspective. What are the biological mechanisms that explain the well-documented association between childhood adversity and adult health impairment? As these causal mechanisms are better elucidated, what can the medical field, specifically, and society, more generally, do to reduce or mitigate the effects of disruptive early-life influences on the origins of lifelong disease? When is the optimal time for those interventions to be implemented?

This technical report addresses these important questions in 3 ways. First, it presents a scientifically grounded, ecobiodevelopmental (EBD) framework to stimulate fresh thinking about the promotion of health and prevention of disease across the lifespan. Second, it applies this EBD framework to better understand the complex relationships among adverse childhood circumstances, toxic stress, brain architecture, and poor physical and mental health well into adulthood. Third, it proposes a new role for pediatricians to promote the development and implementation of science-based strategies to reduce toxic stress in early childhood as a means of preventing or reducing many of society's most complex and enduring problems, which are frequently associated with disparities in learning, behavior, and health. The magnitude of this latter challenge cannot be overstated. A recent technical report from the American Academy of Pediatrics reviewed 58 years of published studies and characterized racial and ethnic disparities in children's health to be extensive, pervasive, persistent, and, in some cases, worsening.[11] Moreover, the report found only 2 studies that evaluated interventions designed to reduce disparities in children's health status and health care that also compared the minority group to a white group, and none used a randomized controlled trial design.

The causal sequences of risk that contribute to demographic differences in educational achievement and physical well-being threaten our country's democratic ideals by undermining the national credo of equal opportunity. Unhealthy communities with too many fast food franchises and liquor stores, yet far too few fresh food outlets and opportunities for physical activity, contribute to an unhealthy population. Unemployment and forced mobility disrupt the social networks that stabilize communities and families and, thereby, lead to higher rates of violence

and school dropout. The purpose of this technical report is to leverage new knowledge from the biological and social sciences to help achieve the positive life outcomes that could be accrued to all of society if more effective strategies were developed to reduce the exposure of young children to significant adversity.

A NEW FRAMEWORK FOR PROMOTING HEALTHY DEVELOPMENT

Advances in our understanding of the factors that either promote or undermine early human development have set the stage for a significant paradigm shift.[12] In simple terms, the process of development is now understood as a function of "nature dancing with nurture over time," in contrast to the longstanding but now outdated debate about the influence of "nature versus nurture."[13] That is to say, beginning prenatally, continuing through infancy, and extending into childhood and beyond, development is driven by an ongoing, inextricable interaction between biology (as defined by genetic predispositions) and ecology (as defined by the social and physical environment)[12,14,15] (see Fig 1).

Building on an ecological model that explains multiple levels of influence on psychological development,[16] and a recently proposed biodevelopmental framework that offers an integrated, science-based approach to coordinated, early childhood policy making and practice across sectors,[17] this technical report presents an EBD framework that draws on a recent report from the Center on the Developing Child at Harvard University to help physicians and policy makers think about how early childhood adversity can lead to lifelong impairments in learning, behavior, and both physical and mental health.[1,6]

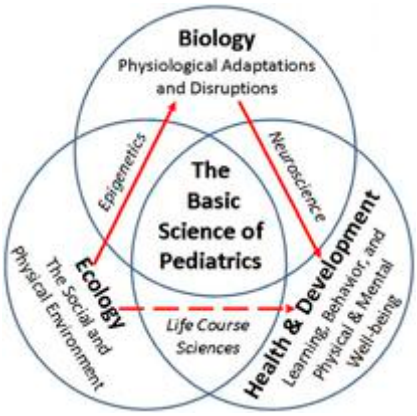

FIGURE 1

The basic science of pediatrics. An emerging, multidisciplinary science of development supports an EBD framework for understanding the evolution of human health and disease across the life span. In recent decades, epidemiology, developmental psychology, and longitudinal studies of early childhood interventions have demonstrated significant associations (hashed red arrow) between the ecology of childhood and a wide range of developmental outcomes and life course trajectories. Concurrently, advances in the biological sciences, particularly in developmental neuroscience and epigenetics, have made parallel progress in beginning to elucidate the biological mechanisms (solid arrows) underlying these important associations. The convergence of these diverse disciplines defines a promising new basic science of pediatrics.

Some of the most compelling new evidence for this proposed framework comes from the rapidly moving field of epigenetics, which investigates the molecular biological mechanisms (such as DNA methylation and histone acetylation) that affect gene expression without altering DNA sequence. For example, studies of maternal care in rats indicate that differences in the quality of nurturing affect neural function in pups and negatively affect cognition and the expression of psychopathology later in life. Moreover, rats whose mothers showed increased levels of licking and grooming during their first week of life also showed less exaggerated stress responses as adults compared with rats who were reared by mothers with a low level of licking and grooming, and the expression of mother-pup interactions in the pups has been demonstrated to be passed on to the next generation.[18–22] This burgeoning area of research is challenging us to look beyond genetic predispositions to examine how environmental influences and early experiences affect when, how, and to what degree different genes are actually activated, thereby elucidating the mechanistic linkages through which gene-environment interaction can affect lifelong behavior, development, and health (see Fig 1).

Additional evidence for the proposed framework comes from insights accrued during the "Decade of the Brain" in the 1990s, when the National Institutes of Health invested significant resources into understanding both normal and pathologic neuronal development and function. Subsequent advances in developmental neuroscience have begun to describe further, in some cases at the molecular and cellular levels, how an integrated, functioning network with billions of neurons and trillions of connections is assembled. Because this network serves as the biological platform for a child's emerging social-emotional, linguistic, and cognitive skills, developmental neuroscience is also beginning to clarify the underlying causal mechanisms that explain the normative process of child development. In a parallel fashion, longitudinal studies that document the long-term consequences of childhood adversity indicate that alterations in a child's ecology can have measurable effects on his or her developmental trajectory, with lifelong consequences for educational achievement, economic productivity, health status, and longevity.[23–27]

The EBD framework described in this article presents a new way to think about the underlying biological mechanisms that explain this robust link between early life adversities (ie, the

new morbidities of childhood) and important adult outcomes. The innovation of this approach lies in its mobilization of dramatic scientific advances in the service of rethinking basic notions of health promotion and disease prevention within a fully integrated, life span perspective from conception to old age.[6] In this context, significant stress in the lives of young children is viewed as a risk factor for the genesis of health-threatening behaviors as well as a catalyst for physiologic responses that can lay the groundwork for chronic, stress-related diseases later in life.

Understanding the Biology of Stress

Although genetic variability clearly plays a role in stress reactivity, early experiences and environmental influences can have considerable impact. Beginning as early as the prenatal period, both animal[28–30] and human[31,32] studies suggest that fetal exposure to maternal stress can influence later stress responsiveness. In animals, this effect has been demonstrated not only in the offspring of the studied pregnancy but also in subsequent generations. The precise biological mechanisms that explain these findings remain to be elucidated, but epigenetic modifications of DNA appear likely to play a role.[31,33,34] Early postnatal experiences with adversity are also thought to affect future reactivity to stress, perhaps by altering the developing neural circuits controlling these neuroendocrine responses.[34,35] Although much research remains to be performed in this area, there is a strong scientific consensus that the ecological context modulates the expression of one's genotype. It is as if experiences confer a "signature" on the genome to authorize certain characteristics and behaviors and to prohibit others. This concept underscores the need for greater understanding of how stress "gets under the skin," as well as the importance of determining what external and internal factors can be mobilized to prevent that embedding process or protect against the consequences of its activation.

Physiologic responses to stress are well defined.[36–38] The most extensively studied involve activation of the hypothalamic-pituitary-adrenocortical axis and the sympathetic-adrenomedullary system, which results in increased levels of stress hormones, such as corticotropin-releasing hormone (CRH), cortisol, norepinephrine, and adrenaline. These changes co-occur with a network of other mediators that include elevated inflammatory cytokines and the response of the parasympathetic nervous system, which counterbalances both sympathetic activation and inflammatory responses. Whereas transient increases in these stress hormones are protective and even essential for survival, excessively high levels or prolonged exposures can be quite harmful or frankly toxic,[39–41] and the dysregulation of this network of physiologic mediators (eg, too much or too little cortisol; too much or too little inflammatory response) can lead to a chronic "wear and tear" effect on multiple organ systems, including the brain.[39–41] This cumulative, stress-induced burden on overall body functioning and the aggregated costs, both physiologic and psychological, required for coping and returning to homeostatic balance, have been referred to as "allostatic load."[38,42–44] The dynamics of these stress-mediating systems are such that their overactivation in the context of repeated or chronic adversity leads to alterations in their regulation.

The National Scientific Council on the Developing Child has proposed a conceptual taxonomy comprising 3 distinct types of stress responses (in contrast to the actual stressors themselves) in young children—positive, tolerable, and toxic—on the basis of postulated differences in their potential to cause enduring physiologic disruptions as a result of the intensity and duration of the response.[17,45] A positive stress response refers to a physiologic state that is brief and mild to moderate in magnitude. Central to the notion of positive stress is the availability of a caring and responsive adult who helps the child cope with the stressor, thereby providing a protective effect that facilitates the return of the stress response systems back to baseline status. Examples of precipitants of a positive stress response in young children include dealing with frustration, getting an immunization, and the anxiety associated with the first day at a child care center. When buffered by an environment of stable and supportive relationships, positive stress responses are a growth-promoting element of normal development. As such, they provide important opportunities to observe, learn, and practice healthy, adaptive responses to adverse experiences.

A tolerable stress response, in contrast to positive stress, is associated with exposure to nonnormative experiences that present a greater magnitude of adversity or threat. Precipitants may include the death of a family member, a serious illness or injury, a contentious divorce, a natural disaster, or an act of terrorism. When experienced in the context of buffering protection provided by supportive adults, the risk that such circumstances will produce excessive activation of the stress response systems that leads to physiologic harm and long-term consequences for health and learning is greatly

reduced. Thus, the essential characteristic that makes this form of stress response tolerable is the extent to which protective adult relationships facilitate the child's adaptive coping and a sense of control, thereby reducing the physiologic stress response and promoting a return to baseline status.

The third and most dangerous form of stress response, toxic stress, can result from strong, frequent, or prolonged activation of the body's stress response systems in the absence of the buffering protection of a supportive, adult relationship. The risk factors studied in the Adverse Childhood Experiences Study[23] include examples of multiple stressors (eg, child abuse or neglect, parental substance abuse, and maternal depression) that are capable of inducing a toxic stress response. The essential characteristic of this phenomenon is the postulated disruption of brain circuitry and other organ and metabolic systems during sensitive developmental periods. Such disruption may result in anatomic changes and/or physiologic dysregulations that are the precursors of later impairments in learning and behavior as well as the roots of chronic, stress-related physical and mental illness. The potential role of toxic stress and early life adversity in the pathogenesis of health disparities underscores the importance of effective surveillance for significant risk factors in the primary health care setting. More important, however, is the need for clinical pediatrics to move beyond the level of risk factor identification and to leverage advances in the biology of adversity to contribute to the critical task of developing, testing, and refining new and more effective strategies for reducing toxic stress and mitigating its effects as early as possible, before irrevocable damage is done. Stated simply, the next chapter of innovation in pediatrics remains to be written, but the outline and plot are clear.

Toxic Stress and the Developing Brain

In addition to short-term changes in observable behavior, toxic stress in young children can lead to less outwardly visible yet permanent changes in brain structure and function.[39,46] The plasticity of the fetal, infant, and early childhood brain makes it particularly sensitive to chemical influences, and there is growing evidence from both animal and human studies that persistently elevated levels of stress hormones can disrupt its developing architecture.[45] For example, abundant glucocorticoid receptors are found in the amygdala, hippocampus, and prefrontal cortex (PFC), and exposure to stressful experiences has been shown to alter the size and neuronal architecture of these areas as well as lead to functional differences in learning, memory, and aspects of executive functioning. More specifically, chronic stress is associated with hypertrophy and overactivity in the amygdala and orbitofrontal cortex, whereas comparable levels of adversity can lead to loss of neurons and neural connections in the hippocampus and medial PFC. The functional consequences of these structural changes include more anxiety related to both hyperactivation of the amygdala and less top-down control as a result of PFC atrophy as well as impaired memory and mood control as a consequence of hippocampal reduction.[47] Thus, the developing architecture of the brain can be impaired in numerous ways that create a weak foundation for later learning, behavior, and health.

Along with its role in mediating fear and anxiety, the amygdala is also an activator of the physiologic stress response. Its stimulation activates sympathetic activity and causes neurons in the hypothalamus to release CRH. CRH, in turn, signals the pituitary to release adrenocorticotropic hormone, which then stimulates the adrenal glands to increase serum cortisol concentrations. The amygdala contains large numbers of both CRH and glucocorticoid receptors, beginning early in life, which facilitate the establishment of a positive feedback loop. Significant stress in early childhood can trigger amygdala hypertrophy and result in a hyperresponsive or chronically activated physiologic stress response, along with increased potential for fear and anxiety.[48,49] It is in this way that a child's environment and early experiences get under the skin.

Although the hippocampus can turn off elevated cortisol, chronic stress diminishes its capacity to do so and can lead to impairments in memory and mood-related functions that are located in this brain region. Exposure to chronic stress and high levels of cortisol also inhibit neurogenesis in the hippocampus, which is believed to play an important role in the encoding of memory and other functions. Furthermore, toxic stress limits the ability of the hippocampus to promote contextual learning, making it more difficult to discriminate conditions for which there may be danger versus safety, as is common in posttraumatic stress disorder. Hence, altered brain architecture in response to toxic stress in early childhood could explain, at least in part, the strong association between early adverse experiences and subsequent problems in the development of linguistic, cognitive, and social-emotional skills, all of which are inextricably intertwined in the wiring of the developing brain.[45]

The PFC also participates in turning off the cortisol response and has an important role in the top-down

regulation of autonomic balance (ie, sympathetic versus parasympathetic effects), as well as in the development of executive functions, such as decision-making, working memory, behavioral self-regulation, and mood and impulse control. The PFC is also known to suppress amygdala activity, allowing for more adaptive responses to potentially threatening or stressful experiences; however, exposure to stress and elevated cortisol results in dramatic changes in the connectivity within the PFC, which may limit its ability to inhibit amygdala activity and, thereby, impair adaptive responses to stress. Because the hippocampus and PFC both play a significant role in modulating the amygdala's initiation of the stress response, toxic stress–induced changes in architecture and connectivity within and between these important areas might account for the variability seen in stress-responsiveness.[50] This can then result in some children appearing to be both more reactive to even mildly adverse experiences and less capable of effectively coping with future stress.[36,37,45,51]

Toxic Stress and the Early Childhood Roots of Lifelong Impairments in Physical and Mental Health

As described in the previous section, stress-induced changes in the architecture of different regions of the developing brain (eg, amygdala, hippocampus, and PFC) can have potentially permanent effects on a range of important functions, such as regulating stress physiology, learning new skills, and developing the capacity to make healthy adaptations to future adversity.[52,53] As the scientific evidence for these associations has become better known and has been disseminated more widely, its implications for early childhood policy and programs have become increasingly appreciated by decision makers across the political spectrum. Notwithstanding this growing awareness, however, discussions about early brain development in policy-making circles have focused almost entirely on issues concerned with school readiness as a prerequisite for later academic achievement and the development of a skilled adult workforce. Within this same context, the health dimension of early childhood policy has focused largely on the traditional components of primary pediatric care, such as immunizations, early identification of sensory impairments and developmental delays, and the prompt diagnosis and treatment of medical problems. That said, as advances in the biomedical sciences have generated growing evidence linking biological disruptions associated with adverse childhood experiences (ACE) to greater risk for a variety of chronic diseases well into the adult years, the need to reconceptualize the health dimension of early childhood policy has become increasingly clear.[1,6] Stated simply, the time has come to expand the public's understanding of brain development and shine a bright light on its relation to the early childhood roots of adult disease and to examine the compelling implications of this growing knowledge base for the future of pediatric practice.

The potential consequences of toxic stress in early childhood for the pathogenesis of adult disease are considerable. At the behavioral level, there is extensive evidence of a strong link between early adversity and a wide range of health-threatening behaviors. At the biological level, there is growing documentation of the extent to which both the cumulative burden of stress over time (eg, from chronic maltreatment) and the timing of specific environmental insults during sensitive developmental periods (eg, from first trimester rubella or prenatal alcohol exposure) can create structural and functional disruptions that lead to a wide range of physical and mental illnesses later in adult life.[1,6] A selective overview of this extensive scientific literature is provided below.

The association between ACE and unhealthy adult lifestyles has been well documented. Adolescents with a history of multiple risk factors are more likely to initiate drinking alcohol at a younger age and are more likely to use alcohol as a means of coping with stress than for social reasons.[54] The adoption of unhealthy lifestyles as a coping mechanism might also explain why higher ACE exposures are associated with tobacco use, illicit drug abuse, obesity, and promiscuity,[55,56] as well as why the risk of pathologic gambling is increased in adults who were maltreated as children.[57] Adolescents and adults who manifest higher rates of risk-taking behaviors are also more likely to have trouble maintaining supportive social networks and are at higher risk of school failure, gang membership, unemployment, poverty, homelessness, violent crime, incarceration, and becoming single parents. Furthermore, adults in this high-risk group who become parents themselves are less likely to be able to provide the kind of stable and supportive relationships that are needed to protect their children from the damages of toxic stress. This intergenerational cycle of significant adversity, with its predictable repetition of limited educational achievement and poor health, is mediated, at least in part, by the social inequalities and disrupted social networks that contribute to fragile families and parenting difficulties.[7,58,59]

The adoption of unhealthy lifestyles and associated exacerbation of socioeconomic inequalities are potent

risk factors for poor health. Up to 40% of early deaths have been estimated to be the result of behavioral or lifestyle patterns,[3] and 1 interpretation of the ACE study data is that toxic stress in childhood is associated with the adoption of unhealthy lifestyles as a coping mechanism.[60] An additional 25% to 30% of early deaths are thought to be attributable to either inadequacies in medical care[3] or socioeconomic circumstances, many of which are known to contribute to health care–related disparities.[61–67]

Beyond its strong association with later risk-taking and generally unhealthy lifestyles, it is critically important to underscore the extent to which toxic stress in early childhood has also been shown to cause physiologic disruptions that persist into adulthood and lead to frank disease, even in the absence of later health-threatening behaviors. For example, the biological manifestations of toxic stress can include alterations in immune function[68] and measurable increases in inflammatory markers,[69–72] which are known to be associated with poor health outcomes as diverse as cardiovascular disease,[69,70,73] viral hepatitis,[74] liver cancer,[75] asthma,[76] chronic obstructive pulmonary disease,[77] autoimmune diseases,[78] poor dental health,[72] and depression.[79–81] Thus, toxic stress in early childhood not only is a risk factor for later risky behavior but also can be a direct source of biological injury or disruption that may have lifelong consequences independent of whatever circumstances might follow later in life. In such cases, toxic stress can be viewed as the precipitant of a physiologic memory or biological signature that confers lifelong risk well beyond its time of origin.[38,42–44]

Over and above its toll on individuals, it is also important to address the enormous social and economic costs of toxic stress and its consequences for all of society. The multiple dimensions of these costs extend from differential levels of civic participation and their impacts on the quality of community life to the health and skills of the nation's workforce and its ability to participate successfully in a global economy. In the realm of learning and behavior, economists argue for early and sustained investments in early care and education programs, particularly for children whose parents have limited education and low income, on the basis of persuasive evidence from cost-benefit analyses that reveal the costs of incarceration and diminished economic productivity associated with educational failure.[82–86] In view of the relatively scarce attention to health outcomes in these long-term follow-up studies, the full return on investments that reduce toxic stress in early childhood is likely to be much higher. Health care expenditures that are paying for the consequences of unhealthy lifestyles (eg, obesity, tobacco, alcohol, and substance abuse) are enormous, and the costs of chronic diseases that may have their origins early in life include many conditions that consume a substantial percentage of current state and federal budgets. The potential savings in health care costs from even small, marginal reductions in the prevalence of cardiovascular disease, hypertension, diabetes, and depression are, therefore, likely to dwarf the considerable economic productivity and criminal justice benefits that have been well documented for effective early childhood interventions.

In summary, the EBD approach to childhood adversity discussed in this report has 2 compelling implications for a full, life span perspective on health promotion and disease prevention. First, it postulates that toxic stress in early childhood plays an important causal role in the intergenerational transmission of disparities in educational achievement and health outcomes. Second, it underscores the need for the entire medical community to focus more attention on the roots of adult diseases that originate during the prenatal and early childhood periods and to rethink the concept of preventive health care within a system that currently perpetuates a scientifically untenable wall between pediatrics and internal medicine.

THE NEED FOR A NEW PEDIATRIC PARADIGM TO PROMOTE HEALTH AND PREVENT DISEASE

In his 1966 Aldrich Award address, Dr Julius Richmond identified child development as the basic science of pediatrics.[87] It is now time to expand the boundaries of that science by incorporating more than 4 decades of transformational research in neuroscience, molecular biology, and genomics, along with parallel advances in the behavioral and social sciences (see Fig 1). This newly augmented, interdisciplinary, basic science of pediatrics offers a promising framework for a deeper understanding of the biology and ecology of the developmental process. More importantly, it presents a compelling opportunity to leverage these rapidly advancing frontiers of knowledge to formulate more effective strategies to enhance lifelong outcomes in learning, behavior, and health.

The time has come for a coordinated effort among basic scientists, pediatric subspecialists, and primary care clinicians to develop more effective strategies for addressing the origins of social class, racial, and ethnic disparities in health and development. To this end, a unified, science-based approach to early childhood policy and practice across multiple sectors (including primary health care, early

care and education, and child welfare, among many others) could provide a compelling framework for a new era in community-based investment in which coordinated efforts are driven by a shared knowledge base rather than distracted by a diversity of traditions, approaches, and funding streams.

Recognizing both the critical value and clear limitations of what can be accomplished within the constraints of an office visit, 21st century pediatrics is well positioned to serve as the primary engine for a broader approach to health promotion and disease prevention that is guided by cutting-edge science and expanded in scope beyond individualized health care.[88,89] The pediatric medical home of the future could offer more than the early identification of concerns and timely referral to available programs, as enhanced collaboration between pediatricians and community-based agencies could be viewed as a vehicle for testing promising new intervention strategies rather than simply improving coordination among existing services. With this goal in mind, science tells us that interventions that strengthen the capacities of families and communities to protect young children from the disruptive effects of toxic stress are likely to promote healthier brain development and enhanced physical and mental well-being. The EBD approach proposed in this article is adapted from a science-based framework created by the Center on the Developing Child at Harvard University to advance early childhood policies and programs that support this vision (see Fig 2).[1] Its rationale, essential elements, and implications for pediatric practice are summarized below.

Broadening the Framework for Early Childhood Policy and Practice

Advances across the biological, behavioral, and social sciences support 2 clear and powerful messages for leaders who are searching for more effective ways to improve the health of the nation.[6] First, current health promotion and disease prevention policies focused largely on adults would be more effective if evidence-based investments were also made to strengthen the foundations of health in the prenatal and early childhood periods. Second, significant reductions in chronic disease could be achieved across the life course by decreasing the number and severity of adverse experiences that threaten the well-being of young children and by strengthening the protective relationships that help mitigate the harmful effects of toxic stress. The multiple domains that affect the biology of health and development—including the foundations of healthy development, caregiver and community capacities, and public and private sector policies and programs—provide a rich array of targeted opportunities for the introduction of innovative interventions, beginning in the earliest years of life.[1]

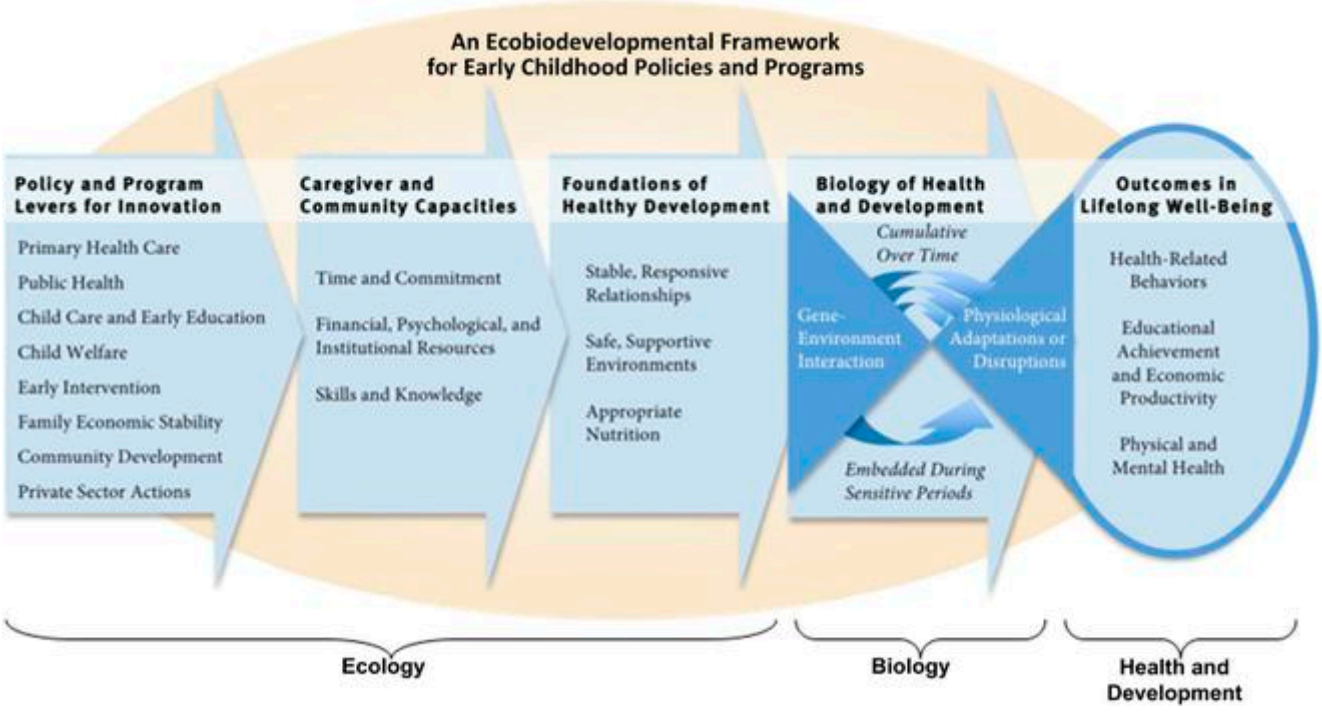

FIGURE 2
An ecobiodevelopmental framework for early childhood policies and programs. This was adapted from ref 1. See text for details.

The biology of health and development explains how experiences and environmental influences get under the skin and interact with genetic predispositions, which then result in various combinations of physiologic adaptation and disruption that affect lifelong outcomes in learning, behavior, and both physical and mental well-being. These findings call for us to augment adult-focused approaches to health promotion and disease prevention by addressing the early childhood origins of lifelong illness and disability.

The foundations of healthy development refers to 3 domains that establish a context within which the early roots of physical and mental well-being are nourished. These include (1) a stable and responsive environment of relationships, which provides young children with consistent, nurturing, and protective interactions with adults to enhance their learning and help them develop adaptive capacities that promote well-regulated stress-response systems; (2) safe and supportive physical, chemical, and built environments, which provide physical and emotional spaces that are free from toxins and fear, allow active exploration without significant risk of harm, and offer support for families raising young children; and (3) sound and appropriate nutrition, which includes health-promoting food intake and eating habits, beginning with the future mother's preconception nutritional status.

Caregiver and community capacities to promote health and prevent disease and disability refers to the ability of family members, early childhood program staff, and the social capital provided through neighborhoods, voluntary associations, and the parents' workplaces to play a major supportive role in strengthening the foundations of child health. These capacities can be grouped into 3 categories: (1) time and commitment; (2) financial, psychological, social, and institutional resources; and (3) skills and knowledge.

Public and private sector policies and programs can strengthen the foundations of health through their ability to enhance the capacities of caregivers and communities in the multiple settings in which children grow up. Relevant policies include both legislative and administrative actions that affect systems responsible for primary health care, public health, child care and early education, child welfare, early intervention, family economic stability (including employment support for parents and cash assistance), community development (including zoning regulations that influence the availability of open spaces and sources of nutritious food), housing, and environmental protection, among others. It is also important to underscore the role that the private sector can play in strengthening the capacities of families to raise healthy and competent children, particularly through supportive workplace policies (such as paid parental leave, support for breastfeeding, and flexible work hours to attend school activities and medical visits).

Defining a Distinctive Niche for Pediatrics Among Multiple Early Childhood Disciplines and Services

Notwithstanding the important goal of ensuring a medical home for all children, extensive evidence on the social determinants of health indicates that the reduction of disparities in physical and mental well-being will depend on more than access to high-quality medical care alone. Moreover, as noted previously, experience tells us that continuing calls for enhanced coordination of effort across service systems are unlikely to be sufficient if the systems are guided by different values and bodies of knowledge and the effects of their services are modest. With these caveats in mind, pediatricians are strategically situated to mobilize the science of early childhood development and its underlying neurobiology to stimulate fresh thinking about both the scope of primary health care and its relation to other programs serving young children and their families. Indeed, every system that touches the lives of children—as well as mothers before and during pregnancy—offers an opportunity to leverage this rapidly growing knowledge base to strengthen the foundations and capacities that make lifelong healthy development possible. Toward this end, explicit investments in the early reduction of significant adversity are particularly likely to generate positive returns.

The possibilities and limitations of well-child care within a multidimensional health system have been the focus of a spirited and enduring discussion within the pediatric community.[88,90,91] Over more than half a century, this dialogue has focused on the need for family-centered, community-based, culturally competent care for children with developmental disabilities, behavior problems, and chronic health impairments, as well as the need for a broader contextual approach to the challenges of providing more effective interventions for children living under conditions of poverty, with or without the additional complications of parental mental illness, substance abuse, and exposure to violence.[10] As the debate has continued, the gap between the call for comprehensive services and the realities of day-to-day practice has remained exceedingly difficult to reduce. Basic recommendations for routine developmental screening and referrals to appropriate community-based services have been particularly difficult

to implement.[92] The obstacles to progress in this area have been formidable at both ends of the process—beginning with the logistical and financial challenges of conducting routine developmental screening in a busy office setting and extending to significant limitations in access to evidence-based services for children and families who are identified as having problems that require intervention.

Despite long-standing calls for an explicit, community-focused approach to primary care, a recent national study of pediatric practices identified persistent difficulties in achieving effective linkages with community-based resources as a major challenge.[92] A parallel survey of parents also noted the limited communication that exists between pediatric practices and community-based services, such as Supplemental Nutrition Program for Women, Infants, and Children; child care providers; and schools.[93] Perhaps most important, both groups agreed that pediatricians cannot be expected to meet all of a child's needs. This challenge is further complicated by the marked variability in quality among community-based services that are available—ranging from evidence-based interventions that clearly improve child outcomes to programs that appear to have only marginal effects or no measurable impacts. Thus, although chronic difficulty in securing access to indicated services is an important problem facing most practicing pediatricians, the limited evidence of effectiveness for many of the options that are available (particularly in rural areas and many states in which public investment in such services is more limited) presents a serious problem that must be acknowledged and afforded greater attention.

At this point in time, the design and successful implementation of more effective models of health promotion and disease prevention for children experiencing significant adversity will require more than advocacy for increased funding. It will require a deep investment in the development, testing, continuous improvement, and broad replication of innovative models of cross-disciplinary policy and programmatic interventions that are guided by scientific knowledge and led by practitioners in the medical, educational, and social services worlds who are truly ready to work together (and to train the next generation of practitioners) in new ways.[88,89] The sheer number and complexity of underaddressed threats to child health that are associated with toxic stress demands bold, creative leadership and the selection of strategic priorities for focused attention. To this end, science suggests that 2 areas are particularly ripe for fresh thinking: the child welfare system and the treatment of maternal depression.

For more than a century, child welfare services have focused on physical safety, reduction of repeated injury, and child custody. Within this context, the role of the pediatrician is focused largely on the identification of suspected maltreatment and the documentation and treatment of physical injuries. Advances in our understanding of the impact of toxic stress on lifelong health now underscore the need for a broader pediatric approach to meet the needs of children who have been abused or neglected. In some cases, this could be provided within a medical home by skilled clinicians with expertise in early childhood mental health. In reality, however, the magnitude of needs in this area generally exceeds the capacity of most primary care practice settings. A report from the Institute of Medicine and National Research Council[15] stated that these needs could be addressed through regularized referrals from the child welfare system to the early intervention system for children with developmental delays or disabilities; subsequent federal reauthorizations of the Keeping Children and Families Safe Act and the Individuals with Disabilities Education Act (Part C) both included requirements for establishing such linkages. The implementation of these federal requirements, however, has moved slowly.

The growing availability of evidence-based interventions that have been shown to improve outcomes for children in the child welfare system[94] underscores the compelling need to transform "child protection" from its traditional concern with physical safety and custody to a broader focus on the emotional, social, and cognitive costs of maltreatment. The Centers for Disease Control and Prevention has taken an important step forward by promoting the prevention of child maltreatment as a public health concern.[95,96] The pediatric community could play a powerful role in leading the call for implementation of the new requirement for linking child welfare to early intervention programs, as well as bringing a strong, science-based perspective to the collaborative development and implementation of more effective intervention models.

The widespread absence of attention to the mother-child relationship in the treatment of depression in women with young children is another striking example of the gap between science and practice that could be reduced by targeted pediatric advocacy.[97] Extensive research has demonstrated the extent to which maternal depression compromises the contingent reciprocity between a mother and her young child that is essential for healthy cognitive, linguistic, social, and emotional development.[98] Despite that well-documented observation, the treatment of depression in women with

young children is typically viewed as an adult mental health service and rarely includes an explicit focus on the mother-child relationship. This serious omission illustrates a lack of understanding of the consequences for the developing brain of a young child when the required "serve and return" reciprocity of the mother-child relationship is disrupted or inconsistent. Consequently, and not surprisingly, abundant clinical research indicates that the successful treatment of a mother's depression does not generally translate into comparable recovery in her young child unless there is an explicit therapeutic focus on their dyadic relationship.[98] Pediatricians are the natural authorities to shed light on this current deficiency in mental health service delivery. Advocating for payment mechanisms that require (or provide incentives for) the coordination of child and parent medical services (eg, through automatic coverage for the parent-child dyad linked to reimbursement for the treatment of maternal depression) offers 1 promising strategy that American Academy of Pediatrics state chapters could pursue. As noted previously, although some medical homes may have the expertise to provide this kind of integrative treatment, most pediatricians rely on the availability of other professionals with specialized skills who are often difficult to find. Whether such services are provided within or connected to the medical home, it is clear that standard pediatric practice must move beyond screening for maternal depression and invest greater energy in securing the provision of appropriate and effective treatment that meets the needs of both mothers and their young children.

The targeted messages conveyed in these 2 examples are illustrative of the kinds of specific actions that offer promising new directions for the pediatric community beyond general calls for comprehensive, family-centered, community-based services. Although the practical constraints of office-based practice make it unlikely that many primary care clinicians will ever play a lead role in the treatment of children affected by maltreatment or maternal depression, pediatricians are still the best positioned among all the professionals who care for young children to provide the public voice and scientific leadership needed to catalyze the development and implementation of more effective strategies to reduce adversities that can lead to lifelong disparities in learning, behavior, and health.

A great deal has been said about how the universality of pediatric primary care makes it an ideal platform for coordinating the services needed by vulnerable, young children and their families. In this respect, the medical home is strategically positioned to play 2 important roles. The first is to ensure that needs are identified, state-of-the-art management is provided as indicated, and credible evaluation is conducted to assess the effects of the services that are being delivered. The second and, ultimately, more transformational role is to mobilize the entire pediatric community (including both clinical specialists and basic scientists) to drive the design and testing of much-needed, new, science-based interventions to reduce the sources and consequences of significant adversity in the lives of young children.[99] To this end, a powerful new role awaits a new breed of pediatricians who are prepared to build on the best of existing community-based services and to work closely with creative leaders from a range of disciplines and sectors to inform innovative approaches to health promotion and disease prevention that generate greater effects than existing efforts.

No other profession brings a comparable level of scientific expertise, professional stature, and public trust—and nothing short of transformational thinking beyond the hospital and office settings is likely to create the magnitude of breakthroughs in health promotion that are needed to match the dramatic advances that are currently emerging in the treatment of disease. This new direction must be part of the new frontier in pediatrics—a frontier that brings cutting-edge scientific thinking to the multidimensional world of early childhood policy and practice for children who face significant adversity. Moving that frontier forward will benefit considerably from pediatric leadership that provides an intellectual and operational bridge connecting the basic sciences of neurobiology, molecular genetics, and developmental psychology to the broad and diverse landscape of health, education, and human services.

SUMMARY

A vital and productive society with a prosperous and sustainable future is built on a foundation of healthy child development. Health in the earliest years—beginning with the future mother's well-being before she becomes pregnant—lays the groundwork for a lifetime of the physical and mental vitality that is necessary for a strong workforce and responsible participation in community life. When developing biological systems are strengthened by positive early experiences, children are more likely to thrive and grow up to be healthy, contributing adults. Sound health in early childhood provides a foundation for the construction of sturdy brain architecture and the achievement of a broad range of skills and learning capacities. Together these constitute the building blocks for a vital and sustainable society that invests in its

human capital and values the lives of its children.

Advances in neuroscience, molecular biology, and genomics have converged on 3 compelling conclusions: (1) early experiences are built into our bodies; (2) significant adversity can produce physiologic disruptions or biological memories that undermine the development of the body's stress response systems and affect the developing brain, cardiovascular system, immune system, and metabolic regulatory controls; and (3) these physiologic disruptions can persist far into adulthood and lead to lifelong impairments in both physical and mental health. This technical report presents a framework for integrating recent advances in our understanding of human development with a rich and growing body of evidence regarding the disruptive effects of childhood adversity and toxic stress. The EBD framework that guides this report suggests that many adult diseases are, in fact, developmental disorders that begin early in life. This framework indicates that the future of pediatrics lies in its unique leadership position as a credible and respected voice on behalf of children, which provides a powerful platform for translating scientific advances into more effective strategies and creative interventions to reduce the early childhood adversities that lead to lifelong impairments in learning, behavior, and health.

CONCLUSIONS

1. Advances in a broad range of interdisciplinary fields, including developmental neuroscience, molecular biology, genomics, epigenetics, developmental psychology, epidemiology, and economics, are converging on an integrated, basic science of pediatrics (see Fig 1).
2. Rooted in a deepening understanding of how brain architecture is shaped by the interactive effects of both genetic predisposition and environmental influence, and how its developing circuitry affects a lifetime of learning, behavior, and health, advances in the biological sciences underscore the foundational importance of the early years and support an EBD framework for understanding the evolution of human health and disease across the life span.
3. The biology of early childhood adversity reveals the important role of toxic stress in disrupting developing brain architecture and adversely affecting the concurrent development of other organ systems and regulatory functions.
4. Toxic stress can lead to potentially permanent changes in learning (linguistic, cognitive, and social-emotional skills), behavior (adaptive versus maladaptive responses to future adversity), and physiology (a hyperresponsive or chronically activated stress response) and can cause physiologic disruptions that result in higher levels of stress-related chronic diseases and increase the prevalence of unhealthy lifestyles that lead to widening health disparities.
5. The lifelong costs of childhood toxic stress are enormous, as manifested in adverse impacts on learning, behavior, and health, and effective early childhood interventions provide critical opportunities to prevent these undesirable outcomes and generate large economic returns for all of society.
6. The consequences of significant adversity early in life prompt an urgent call for innovative strategies to reduce toxic stress within the context of a coordinated system of policies and services guided by an integrated science of early childhood and early brain development.
7. An EBD framework, grounded in an integrated basic science, provides a clear theory of change to help leaders in policy and practice craft new solutions to the challenges of societal disparities in health, learning, and behavior (see Fig 2).
8. Pediatrics provides a powerful yet underused platform for translating scientific advances into innovative early childhood policies, and practicing pediatricians are ideally positioned to participate "on the ground" in the design, testing, and refinement of new models of disease prevention, health promotion, and developmental enhancement beginning in the earliest years of life.

LEAD AUTHORS

Jack P. Shonkoff, MD
Andrew S. Garner, MD, PhD

COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, 2010–2011

Benjamin S. Siegel, MD, Chairperson
Mary I. Dobbins, MD
Marian F. Earls, MD
Andrew S. Garner, MD, PhD
Laura McGuinn, MD
John Pascoe, MD, MPH
David L. Wood, MD

LIAISONS

Robert T. Brown, PhD – *Society of Pediatric Psychology*
Terry Carmichael, MSW – *National Association of Social Workers*
Mary Jo Kupst, PhD – *Society of Pediatric Psychology*
D. Richard Martini, MD – *American Academy of Child and Adolescent Psychiatry*
Mary Sheppard, MS, RN, PNP, BC – *National Association of Pediatric Nurse Practitioners*

CONSULTANT

George J. Cohen, MD

CONSULTANT AND LEAD AUTHOR

Jack P. Shonkoff, MD

STAFF

Karen S. Smith

REFERENCES

1. Center on the Developing Child at Harvard University. The foundations of lifelong health are built in early childhood. Available at: www.developingchild.harvard.edu. Accessed March 8, 2011
2. Knudsen EI, Heckman JJ, Cameron JL, Shonkoff JP. Economic, neurobiological, and behavioral perspectives on building America's future workforce. *Proc Natl Acad Sci U S A*. 2006;103(27):10155–10162
3. McGinnis JM, Williams-Russo P, Knickman JR. The case for more active policy attention to health promotion. *Health Aff (Millwood)*. 2002;21(2):78–93
4. Schor EL, Abrams M, Shea K. Medicaid: health promotion and disease prevention for school readiness. *Health Aff (Millwood)*. 2007;26(2):420–429
5. Wen CP, Tsai SP, Chung WS. A 10-year experience with universal health insurance in Taiwan: measuring changes in health and health disparity. *Ann Intern Med*. 2008; 148(4):258–267
6. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. *JAMA*. 2009;301(21): 2252–2259
7. Braveman P, Barclay C. Health disparities beginning in childhood: a life-course perspective. *Pediatrics*. 2009;124(suppl 3):S163–S175
8. Haggerty RJRK, Pless IB. *Child Health and the Community*. New York, NY: John Wiley and Sons; 1975
9. Committee on Psychosocial Aspects of Child and Family Health; American Academy of Pediatrics. The new morbidity revisited: a renewed commitment to the psychosocial aspects of pediatric care. *Pediatrics*. 2001;108(5):1227–1230
10. Palfrey JS, Tonniges TF, Green M, Richmond J. Introduction: addressing the millennial morbidity—the context of community pediatrics. *Pediatrics*. 2005;115(suppl 4): 1121–1123
11. Flores G, ; Committee On Pediatric Research. Technical report—racial and ethnic disparities in the health and health care of children. *Pediatrics*. 2010;125(4). Available at: www.pediatrics.org/cgi/content/full/125/4/e979
12. Bronfenbrenner U. *The Ecology of Human Development: Experiments by Nature and Design*. Cambridge, MA: Harvard University Press; 1979
13. Sameroff A. A unified theory of development: a dialectic integration of nature and nurture. *Child Dev*. 2010;81(1):6–22
14. Sameroff AJ, Chandler MJ. Reproductive risk and the continuum of caretaking causality. In: Horowitz FD, Hetherington M, Scarr-Salapatek S, Siegel G, eds. *Review of Child Development Research*. Chicago, IL: University of Chicago; 1975:187–244
15. National Research Council, Institute of Medicine, Committee on Integrating the Science of Early Childhood Development; Shonkoff JP, Phillips D, eds. *From Neurons to Neighborhoods: The Science of Early Childhood Development*. Washington, DC: National Academies Press; 2000
16. Bronfenbrenner U. *Making Human Beings Human: Bioecological Perspectives on Human Development*. Thousand Oaks, CA: Sage Publications; 2005
17. Shonkoff JP. Building a new biodevelopmental framework to guide the future of early childhood policy. *Child Dev*. 2010;81(1):357–367
18. Bagot RC, Meaney MJ. Epigenetics and the biological basis of gene × environment interactions. *J Am Acad Child Adolesc Psychiatry*. 2010;49(8):752–771
19. National Scientific Council on the Developing Child. Early experiences can alter gene expression and affect long-term development: working paper #10. Available at: www.developingchild.net. Accessed March 8, 2011
20. Meaney MJ. Epigenetics and the biological definition of gene × environment interactions. *Child Dev*. 2010;81(1):41–79
21. Meaney MJ, Szyf M. Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome. *Dialogues Clin Neurosci*. 2005;7(2):103–123
22. Szyf M, McGowan P, Meaney MJ. The social environment and the epigenome. *Environ Mol Mutagen*. 2008;49(1):46–60
23. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *Am J Prev Med*. 1998;14(4):245–258
24. Schweinhart LJ. *Lifetime Effects: The High/Scope Perry Preschool Study Through Age 40*. Ypsilanti, MI: High/Scope Press; 2005
25. Flaherty EG, Thompson R, Litrownik AJ, et al. Effect of early childhood adversity on child health. *Arch Pediatr Adolesc Med*. 2006;160(12):1232–1238
26. Koenen KC, Moffitt TE, Poulton R, Martin J, Caspi A. Early childhood factors associated with the development of post-traumatic stress disorder: results from a longitudinal birth cohort. *Psychol Med*. 2007;37(2):181–192
27. Flaherty EG, Thompson R, Litrownik AJ, et al. Adverse childhood exposures and reported child health at age 12. *Acad Pediatr*. 2009;9(3):150–156
28. Cottrell EC, Seckl JR. Prenatal stress, glucocorticoids and the programming of adult disease. *Front Behav Neurosci*. 2009;3:19
29. Darnaudéry M, Maccari S. Epigenetic programming of the stress response in male and female rats by prenatal restraint stress. *Brain Res Brain Res Rev*. 2008;57(2):571–585
30. Seckl JR, Meaney MJ. Glucocorticoid "programming" and PTSD risk. *Ann N Y Acad Sci*. 2006;1071:351–378
31. Oberlander TF, Weinberg J, Papsdorf M, Grunau R, Misri S, Devlin AM. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR3C1) and infant cortisol

stress responses. *Epigenetics*. 2008;3(2):97–106

32. Brand SR, Engel SM, Canfield RL, Yehuda R. The effect of maternal PTSD following in utero trauma exposure on behavior and temperament in the 9-month-old infant. *Ann N Y Acad Sci*. 2006;1071:454–458
33. Murgatroyd C, Patchev AV, Wu Y, et al. Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nat Neurosci*. 2009;12(12):1559–1566
34. Roth TL, Lubin FD, Funk AJ, Sweatt JD. Lasting epigenetic influence of early-life adversity on the BDNF gene. *Biol Psychiatry*. 2009;65(9):760–769
35. Szyf M. The early life environment and the epigenome. *Biochim Biophys Acta*. 2009;1790(9):878–885
36. Compas BE. Psychobiological processes of stress and coping: implications for resilience in children and adolescents—comments on the papers of Romeo & McEwen and Fisher et al. *Ann N Y Acad Sci*. 2006;1094:226–234
37. Gunnar M, Quevedo K. The neurobiology of stress and development. *Annu Rev Psychol*. 2007;58:145–173
38. McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev*. 2007;87(3):873–904
39. McEwen BS. Stressed or stressed out: what is the difference? *J Psychiatry Neurosci*. 2005;30(5):315–318
40. McEwen BS, Seeman T. Protective and damaging effects of mediators of stress. Elaborating and testing the concepts of allostasis and allostatic load. *Ann N Y Acad Sci*. 1999;896:30–47
41. McEwen BS. Protective and damaging effects of stress mediators. *N Engl J Med*. 1998;338(3):171–179
42. Korte SM, Koolhaas JM, Wingfield JC, McEwen BS. The Darwinian concept of stress: benefits of allostasis and costs of allostatic load and the trade-offs in health and disease. *Neurosci Biobehav Rev*. 2005;29(1):3–38
43. McEwen BS. Mood disorders and allostatic load. *Biol Psychiatry*. 2003;54(3):200–207
44. McEwen BS. Stress, adaptation, and disease. Allostasis and allostatic load. *Ann N Y Acad Sci*. 1998;840:33–44
45. National Scientific Council on the Developing Child. *Excessive Stress Disrupts the Architecture of the Developing Brain: Working Paper #3*. Available at: developingchild.harvard.edu/resources/reports_and_working_papers/. Accessed March 8, 2011
46. McEwen BS. Protective and damaging effects of stress mediators: central role of the brain. *Dialogues Clin Neurosci*. 2006;8(4):367–381
47. McEwen BS, Gianaros PJ. Stress- and allostasis-induced brain plasticity. Annu Rev Med. 2011;62:431–445
48. National Scientific Council on the Developing Child. Persistent fear and anxiety can affect young children's learning and development: working paper #9. Available at: www.developingchild.net. Accessed March 8, 2011
49. Tottenham N, Hare TA, Quinn BT, et al. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Dev Sci*. 2010;13(1):46–61
50. Boyce WT, Ellis BJ. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Dev Psychopathol*. 2005;17(2):271–301
51. Francis DD. Conceptualizing child health disparities: a role for developmental neurogenomics. *Pediatrics*. 2009;124(suppl 3):S196–S202
52. Juster RP, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci Biobehav Rev*. 2010;35(1):2–16
53. McEwen BS, Gianaros PJ. Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Ann N Y Acad Sci*. 2010;1186:190–222
54. Rothman EF, Edwards EM, Heeren T, Hingson RW. Adverse childhood experiences predict earlier age of drinking onset: results from a representative US sample of current or former drinkers. *Pediatrics*. 2008;122(2). Available at: www.pediatrics.org/cgi/content/full/122/2/e298
55. Anda RF, Croft JB, Felitti VJ, et al. Adverse childhood experiences and smoking during adolescence and adulthood. *JAMA*. 1999;282(17):1652–1658
56. Anda RF, Felitti VJ, Bremner JD, et al. The enduring effects of abuse and related adverse experiences in childhood. A convergence of evidence from neurobiology and epidemiology. *Eur Arch Psychiatry Clin Neurosci*. 2006;256(3):174–186
57. Scherrer JF, Xian H, Kapp JM, et al. Association between exposure to childhood and lifetime traumatic events and lifetime pathological gambling in a twin cohort. *J Nerv Ment Dis*. 2007;195(1):72–78
58. Wickrama KA, Conger RD, Lorenz FO, Jung T. Family antecedents and consequences of trajectories of depressive symptoms from adolescence to young adulthood: a life course investigation. *J Health Soc Behav*. 2008;49(4):468–483
59. Kahn RS, Brandt D, Whitaker RC. Combined effect of mothers' and fathers' mental health symptoms on children's behavioral and emotional well-being. *Arch Pediatr Adolesc Med*. 2004;158(8):721–729
60. Felitti VJ. Adverse childhood experiences and adult health. *Acad Pediatr*. 2009;9(3):131–132
61. Althoff KN, Karpati A, Hero J, Matte TD. Secular changes in mortality disparities in New York City: a reexamination. *J Urban Health*. 2009;86(5):729–744
62. Cheng TL, Jenkins RR. Health disparities across the lifespan: where are the children? *JAMA*. 2009;301(23):2491–2492
63. DeVoe JE, Tillotson C, Wallace LS. Uninsured children and adolescents with insured parents. *JAMA*. 2008;300(16):1904–1913
64. Due P, Merlo J, Harel-Fisch Y, et al. Socioeconomic inequality in exposure to bullying during adolescence: a comparative, cross-sectional, multilevel study in 35 countries. *Am J Public Health*. 2009;99(5):907–914
65. Reid KW, Vittinghoff E, Kushel MB. Association between the level of housing instability, economic standing and health care access: a meta-regression. *J Health Care Poor Underserved*. 2008;19(4):1212–1228
66. Stevens GD, Pickering TA, Seid M, Tsai KY. Disparities in the national prevalence of a quality medical home for children with asthma. *Acad Pediatr*. 2009;9(4):234–241
67. Williams DR, Sternthal M, Wright RJ. Social determinants: taking the social context of asthma seriously. *Pediatrics*. 2009;123(suppl 3):S174–S184
68. Bierhaus A, Wolf J, Andrassy M, et al. A mechanism converting psychosocial stress into mononuclear cell activation. *Proc Natl Acad Sci U S A*. 2003;100(4):1920–1925
69. Araújo JP, Lourenço P, Azevedo A, et al. Prognostic value of high-sensitivity C-reactive protein in heart failure: a systematic review. *J Card Fail*. 2009;15(3):256–266
70. Galkina E, Ley K. Immune and inflammatory mechanisms of atherosclerosis (*). *Annu Rev Immunol*. 2009;27:165–197
71. Miller GE, Chen E. Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. *Psychol Sci*. 2010;21(6):848–856
72. Poulton R, Caspi A, Milne BJ, et al. Association between children's experience of socioeconomic disadvantage and adult health: a life-course study. *Lancet*. 2002;360(9346):1640–1645
73. Ward JR, Wilson HL, Francis SE, Crossman DC, Sabroe I. Translational mini-review series on immunology of vascular disease: inflammation, infections and Toll-like

receptors in cardiovascular disease. *Clin Exp Immunol*. 2009;156(3):386–394

74. Heydtmann M, Adams DH. Chemokines in the immunopathogenesis of hepatitis C infection. *Hepatology*. 2009;49(2):676–688
75. Berasain C, Castillo J, Perugorria MJ, Latasa MU, Prieto J, Avila MA. Inflammation and liver cancer: new molecular links. *Ann N Y Acad Sci*. 2009;1155:206–221
76. Chen E, Miller GE. Stress and inflammation in exacerbations of asthma. *Brain Behav Immun*. 2007;21(8):993–999
77. Yao H, Rahman I. Current concepts on the role of inflammation in COPD and lung cancer. *Curr Opin Pharmacol*. 2009;9(4):375–383
78. Li M, Zhou Y, Feng G, Su SB. The critical role of Toll-like receptor signaling pathways in the induction and progression of autoimmune diseases. *Curr Mol Med*. 2009;9(3):365–374
79. Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Arch Gen Psychiatry*. 2008;65(4):409–415
80. Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. Childhood maltreatment predicts adult inflammation in a life-course study. *Proc Natl Acad Sci U S A*. 2007;104(4):1319–1324
81. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171–186
82. Cuhna F, Heckman JJ, Lochner LJ, Masterov DV. Interpreting the evidence on life cycle skill formation. In: Hanushek EA, Welch F, eds. *Handbook of the Economics of Education*. Amsterdam, Netherlands: North-Holland; 2006:697–812
83. Heckman JJ, Stixrud J, Urzua S. The effects of cognitive and non-cognitive abilities on labor market outcomes and social behavior. *J Labor Econ*. 2006;24:411–482
84. Heckman JJ. Role of income and family influence on child outcomes. Ann N Y Acad Sci. 2008;1136:307–323
85. Heckman JJ. The case for investing in disadvantaged young children. Available at: www.firstfocus.net/sites/default/files/r.2008-9.15.ff_.pdf. Accessed March 8, 2011
86. Heckman JJ, Masterov DV. The productivity argument for investing in young children. Available at: http://jenni.uchicago.edu/human-inequality/papers/Heckman_final_all_wp_2007-03-22c_jsb.pdf. Accessed March 8, 2011
87. Richmond JB. Child development: a basic science for pediatrics. *Pediatrics*. 1967;39(5):649–658
88. Leslie LK, Slaw KM, Edwards A, Starmer AJ, Duby JC, ; Members of Vision of Pediatrics 2020 Task Force. Peering into the future: pediatrics in a changing world. *Pediatrics*. 2010;126(5):982–988
89. Starmer AJ, Duby JC, Slaw KM, Edwards A, Leslie LK, ; Members of Vision of Pediatrics 2020 Task Force. Pediatrics in the year 2020 and beyond: preparing for plausible futures. *Pediatrics*. 2010;126(5):971–981
90. Halfon N, DuPlessis H, Inkelas M. Transforming the U.S. child health system. *Health Aff (Millwood)*. 2007;26(2):315–330
91. Schor EL. The future pediatrician: promoting children's health and development. *J Pediatr*. 2007;151(suppl 5):S11–S16
92. Tanner JL, Stein MT, Olson LM, Frintner MP, Radecki L. Reflections on well-child care practice: a national study of pediatric clinicians. *Pediatrics*. 2009;124(3):849–857
93. Radecki L, Olson LM, Frintner MP, Tanner JL, Stein MT. What do families want from well-child care? Including parents in the rethinking discussion. *Pediatrics*. 2009;124(3):858–865
94. Fisher PA, Gunnar MR, Dozier M, Bruce J, Pears KC. Effects of therapeutic interventions for foster children on behavioral problems, caregiver attachment, and stress regulatory neural systems. *Ann N Y Acad Sci*. 2006;1094:215–225
95. Mercy JA, Saul J. Creating a healthier future through early interventions for children. *JAMA*. 2009;301(21):2262–2264
96. Middlebrooks JS, Audage NC. The effects of childhood stress on health across the lifespan. Available at: www.cdc.gov/ncipc/pubres/pdf/Childhood_Stress.pdf. Accessed July 20, 2009
97. Earls MF, ; Committee on Psychosocial Aspects of Child and Family Health; American Academy of Pediatrics. Incorporating recognition and management of perinatal and postpartum depression into pediatric practice. *Pediatrics*. 2010;126(5):1032–1039
98. Center on the Developing Child at Harvard University. Maternal depression can undermine the development of young children: working paper #8. Available at: www.developingchild.harvard.edu. Accessed March 8, 2011
99. Shonkoff J. Protecting brains, not simply stimulating minds. *Science*. 2011;333(6045):982–983

The Lifelong Effects of Early Childhood Adversity and Toxic Stress

Jack P. Shonkoff, Andrew S. Garner, THE COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, COMMITTEE ON EARLY CHILDHOOD, ADOPTION, AND DEPENDENT CARE, AND SECTION ON DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS, Benjamin S. Siegel, Mary I. Dobbins, Marian F. Earls, Andrew S. Garner, Laura McGuinn, John Pascoe and David L. Wood

Pediatrics 2012;129;e232; originally published online December 26, 2011; DOI: 10.1542/peds.2011-2663