Neuroscience, Molecular Biology, and the Childhood Roots of Health Disparities: Building a New Framework for Health Promotion and Disease Prevention

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Neuroscience, Molecular Biology, and the Childhood Roots of Health Disparities

Building a New Framework for Health Promotion and Disease Prevention

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A scientific consensus is emerging that the origins of adult disease are often found among developmental and biological disruptions occurring during the early years of life. These early experiences can affect adult health in 2 ways—either by cumulative damage over time or by the biological embedding of adversities during sensitive developmental periods. In both cases, there can be a lag of many years, even decades, before early adverse experiences are expressed in the form of disease. From both basic research and policy perspectives, confronting the origins of disparities in physical and mental health early in life may produce greater effects than attempting to modify health-related behaviors or improve access to health care in adulthood.

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ADVANCES IN DEVELOPMENTAL biology are building an increasingly persuasive case for a new way of thinking about health promotion and disease prevention that focuses on the origins of persistent disparities in morbidity and mortality in the early years of life. Central to this framework is an increasing interest in the extent to which early experiences and exposures are biologically embedded and have lifelong consequences.

The following example illustrates how the translation of this evolving science base into innovative policy can generate new approaches to reducing the burden of preventable disease.

In 2008, the American Academy of Pediatrics issued a report to address a "new urgency given the current epidemic of childhood obesity with the subsequent increasing risk of type 2 diabetes mellitus, hypertension, and cardiovascular disease in older children and adults."[1] The report underscored the need for a more proactive approach in childhood to the prevention of cardiovascular disease through enhanced adherence to dietary guidelines, increasing physical activity, and consideration of pharmacologic treatment of dyslipidemia beginning as early as age 8 years. What the report did not consider is the idea, based on growing evidence of the cardiovascular sequelae of early life adversity, that new interventions to reduce significant stress in early childhood may be a more appropriate strategy for preventing adult heart disease than the off-label administration of statins to school-aged children. In this article, we explore the scientific validity of the proposition that reducing significant disadvantage early in life may be a powerful strategy for reducing the population-level burden of chronic morbidity and premature death.

Emergence of a New Scientific Approach for Health Policy

Differences in health outcomes related to social class and other markers of disadvantage have been well documented across a broad range of cultures, as well as in societies with a variety of health care systems.[2-4] Despite the unassailable reliability of this robust association, the elucidation of precise causal mechanisms linking adversity to health status remains elusive, and effective policy remedies are not readily apparent.[5]

Notwithstanding the fundamental importance of high-quality medical care for those who are ill, the limited capacity of high-quality care to reduce socioeconomic and racial disparities in health outcomes is clear. Central to this understanding is the persistence of social class gradients in disease prevalence and mortality rates in nations that provide universal access to health care services.[6] Some critics have responded by suggesting greater focus on inequalities in service utilization and differential treatment by the health care system. Others have called for greater attention to the role of broader social and economic influences on health, although the task of translating this perspective into concrete policy initiatives has generated more rhetoric than action. While clinicians apply advances in the biomedical

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sciences to transform their capacity to treat patients who are sick, policy makers who are interested in population health would be well served by a deeper understanding of the underlying biology of early adversity.

For much of the 20th century, adult conditions such as coronary heart disease, stroke, diabetes, and cancer were regarded solely as products of adult behavior and lifestyles.[7] By the century's end, however, an extensive body of evidence linked adult chronic disease to processes and experiences occurring decades before, in some cases as early as intrauterine life, across a wide range of impairments. Longitudinal studies have demonstrated that pulmonary disease in adulthood is commonly associated with a history of respiratory illnesses in childhood.[8] Intrauterine exposure to diethylstilbestrol was discovered to underlie vaginal and cervical cancers in young women.[9] Prenatal processes have been associated with the later manifestations of schizophrenia[10,11] and autism,[12,13] and early social environments have been shown to play formative roles in cognitive and socioemotional development.[14] Researchers have also found that cardiovascular disease in later life can be linked to nutritional deficits and growth impairments in the prenatal period.[15-18]

Although full elucidation of the causal mechanisms that account for these associations awaits further investigation, the relation between early life conditions and long-term health outcomes remains robust. A comprehensive review of that evidence base and detailed analysis of its policy implications are beyond the scope of a single report. The purpose of this article is to propose a framework for increased collaborative work in this area, based on the assertion that the promotion of health and prevention of disease in adults begins in the early years of life.

Investigators have postulated that early experience can affect adult health in at least 2 ways—by accumulating damage over time or by the biological embedding of adversities during sensitive developmental periods.[7,19] In both cases, there can be a lag of many years, even decades, before early adverse experiences are expressed in the form of illness. If the damage occurs through a cumulative process, chronic diseases can be seen as the products of repeated encounters with both psychologically and physically stressful experiences. When exposures occur during sensitive periods of development, their effects can become permanently incorporated into regulatory physiological processes, and subsequent adult disease may be viewed as the latent outcome of critical events that occurred during early periods of special susceptibility.

Cumulative Exposures to Stressful Experiences. Strong associations have been shown between retrospective adult reports of increasing numbers of traumatic childhood events with greater prevalence of a wide array of health impairments, including coronary artery disease, chronic pulmonary disease, cancer, alcoholism, depression, and drug abuse,[20,21] as well as overlapping mental health problems,[22] teen pregnancies,[23] and cardiovascular risk factors such as obesity, physical inactivity, and smoking.[24] Other longitudinal studies have found similar linkages.[25-28] Recent prospective data have reinforced this association, including evidence that depressed adults with a documented history of maltreatment in childhood are twice as likely to have clinically relevant elevations of high-sensitivity C-reactive protein levels compared with controls, whereas individuals with depression and no history of maltreatment showed nonsignificant increases in this biomarker of greater risk of cardiovascular disease.[29]

Another body of research has suggested that "weathering" of the body under persistent adversity (ie, the increased wear and tear induced by stressful experiences that overuse and dysregulate pathways normally used for adaptation to threat) reflects an acceleration of normal aging processes.[30-32] African Americans, for example, experience earlier deteriorations of health in a cumulative fashion, leading to progressively larger health disparities with age and a life expectancy that is 4 to 6 years less than for whites.[33] One hypothesized causal mechanism is the persistence of stress associated with discrimination that accelerates the aging process.[34]

Cumulative-exposure explanations of chronic adult disease are consistent with research that addresses the breakdown of physiological steady state under conditions of chronic challenge—a phenomenon referred to as "allostatic load."[35] Under such circumstances, activation of stress management systems in the brain results in a highly integrated repertoire of responses involving secretion of stress hormones, increases in heart rate and blood pressure, protective mobilization of nutrients, redirection of blood perfusion to the brain, and induction of vigilance and fear.[36] These neurobiological responses are essential and generally protective, but when activated persistently under circumstances of chronic or overwhelming adversity, they can become pathogenic.[37,38] Within this context, extensive documentation of the disproportionate exposure of low-income children to environmental stressors, traumatic experiences, and family chaos[39-41] takes on a greater sense of urgency. This threat is underscored even further by recent evidence of higher levels of physiological and emotional dysregulation in this high-risk group.[42]

Latent Effects of Adversity During Sensitive Periods. A considerable body of research also suggests that adult disease and risk factors for poor health can be embedded biologically during sensitive periods in which the developing brain is more receptive to a variety of environmental signals, whether positive or negative.[43] For example, poor living conditions early in life (eg, inadequate nutrition, other constraints on fetal and infant growth, and recurrent infections) are associated with increased rates of cardiovascular, respiratory, and psychiatric diseases in adulthood.[15,44-48] Investigators have also documented an association between lower birth weight and several risk factors for heart disease, including hypertension, central body fat distribution, insulin resistance, metabolic syndrome, and type 2 diabetes.[15]

These findings are supported by evidence from both animal and human studies. For example, lower birth weight due to intrauterine growth restriction in rats has been associated with higher blood pressure,[49] and studies of human infants have linked poor intrauterine growth to deficits in neural control of the heart[50] and hypertension.[51] Early experiences of child maltreatment and poverty have been associated with heightened immune responses in adulthood that are known risk factors for the development of cardiovascular disease, diabetes, asthma, and chronic lung disease.[52,53] So-called natural experiments have provided additional, corroborating support for this association. Individuals exposed to severe nutritional deficits in utero during the Dutch famine of 1944, for example, showed a higher prevalence of coronary heart disease when evaluated 50 years later.[46] Similarly, children in a Helsinki birth cohort evacuated to temporary foster care during World War II have shown higher rates of both cardiovascular morbidity and symptoms of depression compared with their nonevacuated peers.[54,55]

The Central Role of the Brain. As the primary organ of stress and adaptation, the brain is both vulnerable and adaptable. It interprets and regulates behavioral, neuroendocrine, autonomic, and immunological responses to adverse events, serves as a target of acute and chronic psychosocial and physical stress, and changes both structurally and functionally as a result of significant adversity.[35,56] Animal models have provided considerable insights into differential responsivity to stress among different brain regions, including the hippocampus, amygdala, and prefrontal cortex. Studies have shown both adaptive and maladaptive effects of stress hormones throughout the life course, with early life events influencing lifelong patterns of emotionality and stress responsiveness as well as altering the rate of brain and body aging. Stress-induced remodeling of neuronal structure and connectivity in these regions alters behavioral and physiological responses, including anxiety, aggression, mental flexibility, memory, and other cognitive processes.[56]

New imaging techniques are driving rapid advances in knowledge about how the human brain changes with experience. Recent findings include the association of reduced hippocampal volume with prolonged perceived stress[57] as well as with diagnosed conditions such as diabetes, major depression, Cushing disease, and posttraumatic stress disorder.[58,59] In contrast, physical activity and fitness in elderly individuals is associated with increased hippocampal volume and better memory function,[60] as well as greater activation of prefrontal cortical activity and enhanced executive function.[61,62]

The prefrontal cortex, which is involved in executive functions such as working memory and behavioral inhibition, as well as top-down control of autonomic nervous system balance, has been found to be smaller in individuals with major depression[63] and in individuals who self-report lower socioeconomic status.[64] In addition, the prefrontal cortex has been shown to be impaired transiently by increased levels of perceived stress in medical students studying for a board examination.[65] Functional activation of the prefrontal cortex is also associated with blood pressure responses,[66] whereas greater functional activation of the amygdala is associated with the development of atherosclerosis.[66]

The Complexity of Heterogeneous Response. Although evidence continues to accumulate supporting both cumulative and latent effect models of how early adversities may amplify long-term disease risks, studies also reveal compelling individual differences in the magnitude or even direction of such effects. One investigation, for example, found that 61% of individuals reporting significant emotional abuse in childhood developed major depression as adults (compared with 18.5% of those reporting no emotional abuse), yet nearly 2 of 5 emotionally abused individuals had no such impairment.[67]

Similarly, although the risk of coronary heart disease is nearly 4 times more frequent among adults with birth weights less than 2500 g (15%) compared with individuals with birth weights greater than 4000 g (4%), these risk ratios tend to obscure the counterobservation that 85% of low-birth-weight infants did not develop later heart disease.[68] Such marked heterogeneity in the longitudinal consequences of early life experiences suggests underlying differences in vulnerability that may moderate these associations.[56,69,70] Evidence for such effect modification has been derived from studies of gene-environment interaction in which allelic variations in neuroregulatory and transcription factor–encoding genes are associated with greater risks related to early stressors[71-74] as well as from studies showing that individual differences in neurobiological sensitivity to social environments can bias outcomes both positively and negatively, depending on the protective vs injurious nature of early exposures.[37,72,75-77]

Biological Embedding. The epigenetic pathways by which adversity is transmuted into lasting alterations in disease risk are an example of the broader adaptive processes through which early influences affect the regulation of biological systems.[78] These adaptations are evolved mechanisms that monitor the environment, beginning during the prenatal period, to adjust set points within important brain circuits. For example, a fetus in an intrauterine environment characterized by poor nutrition may undergo energy-sparing, metabolic changes that are designed to be adaptive in a postnatal environment of food scarcity. While these metabolic changes may be beneficial in the short run, later problems can arise when the adaptive prediction turns out to be wrong, and the early childhood environment is characterized by energy abundance, a carbohydrate-rich diet, and a sedentary lifestyle.[79] In such circumstances, according to some theorists, the risk of later obesity and other metabolic disorders can begin very early in life.[80]

Children from families and communities with low income and low education levels may be especially vulnerable to the biological embedding of disease

risk because of their disproportionate exposure to highly stressful influences such as neighborhood violence, dysfunctional schools, personal maltreatment, household chaos, and absent parents.[81,82] These risk factors are often compounded by limited access to healthful foods and high consumption of energy-dense products[83,84] that are contributing to the increasing prevalence of obesity and diabetes, particularly among low-income children. Children living in disadvantaged environments are also more likely to experience conflictive and punitive parental behavior[81,85,86] as well as relatively fewer positive experiences such as reading, interactive conversation, and after-school activities.[87] In some cases, the cumulative burden of multiple risk factors early in life may limit the effectiveness of later interventions, thereby making it impossible to completely reverse the neurobiological and health consequences of growing up poor.[7]

Current research is charting new territory in understanding the linkages between differential childhood experiences and several aspects of brain development within regions tied to the regulation of emotion and social behavior, reasoning capacity, language skills, and stress reactivity.[54] Children from lower socioeconomic backgrounds show heightened activation of stress-responsive systems[88,89] and emerging evidence suggests that differences in parenting related to income and education—as mediated through parent-child interaction, exposure to new vocabulary, and stability of responsiveness—can alter the maturation of selected brain areas, such as the prefrontal cortex.[90,91] Animal models of early, stress-related changes in brain circuitry show that such changes can persist into adult life and alter emotional states, decision-making capacities, and bodily processes that contribute to emotional instability, substance abuse, aggression, obesity, and stress-related disorders.[92,93]

Moreover, although early adversity can lead to greater vulnerability later in life, positive experiences can decrease such risk. For example, capitalizing on naturally occurring variation in maternal caretaking behaviors in rats, studies have demonstrated that pups experiencing more intensive and responsive maternal care have lower levels of the stress hormone corticosterone. This predisposition to a more modest stress response continues into adult life and is transmitted to the second and third generations of offspring.[94,95] Such effects are likely to extend to humans and nonhuman primates as well and to involve modifications in the expression of glucocorticoid receptors in brain regions mediating affect and cognition as well as neurotrophic factors operating throughout the body.[96,97] Such alterations of stress systems across generations—caused not by genetic inheritance but by early experiences—are facilitated by epigenetic changes in DNA methylation and histone modification of chromatin in response to environmental cues that, in turn, influence how the next generation's genes are expressed.[94,98-100]

Although much of this research is based on animal experiments, experience-related variation in gene expression may offer important clues about how disparities in early exposure to adversity can change adult health outcomes in humans. A recent report on human brain autopsy material from individuals who experienced childhood abuse revealed changes in DNA methylation related to the glucocorticoid receptor that mirrors changes reported in these same types of receptors in brains of rodents that experienced poor maternal care.[96]

Complexity of Early Childhood Stress as a Policy Issue

Despite increasing evidence of the long-term effects of early adversity on lifelong health, little attention has been paid to the development of health promotion and disease prevention strategies based on the reduction of significant stressors affecting everyday life for vulnerable young children and their parents. This potential shortsightedness may in part be the result of a generalized misunderstanding about the nature and effects of childhood stress. For example, although mastery of relatively minor adversity by children is viewed as a necessary prerequisite for developing resilience to later challenges, the public is less aware that levels of stress associated with excessive, persistent, and/or uncontrollable adversity, without the buffering protection of stable adult support, are associated with disruptive effects on multiple organ systems that can lead to lifelong disease. This is an area in which further scientific advances linked to enhanced public understanding could inform innovative policy approaches.

The National Scientific Council on the Developing Child proposed the following simple taxonomy to describe 3 categories of stress experience—positive, tolerable, and toxic—that can affect the development of young children.[101] In this framework, stress refers to the physiological expression of the stress response system, not the nature of the stressor nor the distinction between objectively measured and perceived stress. Although much work remains to elucidate the underlying causal mechanisms, the conceptual basis of this model is grounded in well-established core biological principles.

Positive stress is characterized by moderate, short-lived increases in heart rate, blood pressure, and stress hormone levels. Precipitants include the challenges of dealing with frustration, receiving an injected immunization, and other normative experiences. The essential nature of positive stress is that it is an important aspect of healthy development that is experienced in the context of stable and supportive relationships that facilitate adaptive responses, which, in turn, restore the stress response system to baseline status.

Tolerable stress refers to a physiological state that could potentially disrupt brain architecture (eg, through cortisol-induced disruption of neural circuits or neuronal death in the hippocampus) but is buffered by supportive relationships that facilitate adaptive coping. Precipitants include the death or serious illness of a loved one, homelessness, or a natural disaster. The defining characteristic of tolerable stress is that it occurs within a time-limited period, during

which protective relationships help to bring the body's stress-response systems back to baseline, thereby giving the brain time to recover from potentially damaging effects.

Toxic stress refers to strong, frequent, and/or prolonged activation of the body's stress-response systems in the absence of the buffering protection of adult support. Major risk factors include extreme poverty, recurrent physical and/or emotional abuse, chronic neglect, severe maternal depression, parental substance abuse, and family violence. The defining characteristic of toxic stress is that it disrupts brain architecture, affects other organ systems, and leads to stress-management systems that establish relatively lower thresholds for responsiveness that persist throughout life, thereby increasing the risk of stress-related disease and cognitive impairment well into the adult years.

This simple taxonomy provides a useful approach for helping policy makers differentiate normative life challenges that are growth-promoting from significant adversities that threaten long-term health and development. As such, it provides a useful framework for considering earlier opportunities for preventive intervention.

Health Promotion and Disease Prevention Within a Science-Based, Early Childhood Framework

Current efforts related to health promotion and disease prevention in most economically developed countries are generally guided by 3 strategies. The first focuses on the provision of immunizations, anticipatory guidance, and early identification and management of problems in the context of primary health care for children who have access to medical services, as well as public policies designed to reduce injuries, such as mandatory seat belt laws. The second approach is directed toward programs that encourage health-promoting behaviors in adults, such as better nutrition and increased exercise. The third strategy is focused on reducing health-threatening behaviors in adults, such as smoking, excessive alcohol consumption, illicit substance abuse, and risk-taking behaviors associated with sexually transmitted diseases. The first approach is embedded largely in a model of individually focused medical services for children. The second and third strategies are grounded in a theory of change based on the capacity to modify the behavior of adults.

Although the potential benefits of health education at any age should not be underestimated, the ultimate impact of policies designed to improve population health through efforts that begin in the adult years is limited by 3 important constraints. First, it is burdened by the increasing difficulty of changing behavior and lifestyles as individuals grow older. Second, it faces the difficult challenge of overcoming biological vulnerabilities that may have been embedded physiologically as a result of early adversity and that might have been prevented by changing the environments in which young children live. Third, by addressing adult behaviors, instead of the conditions faced by children and their families, such policies shift the locus of responsibility toward individuals whose health risks have been influenced much earlier in life and away from the potentially modifiable circumstances that shaped them in the first place.

These limitations of adult-focused health promotion efforts lead to the compelling hypothesis that a fundamental transformation in the circumstances of children who experience significant adversity early in life could not only affect their own individual well-being but also improve societal health and longevity. To this end, an integrated developmental science of health, learning, and behavior could support several implications for health policy and clinical practice. The following are 3 examples worthy of thoughtful consideration.

Adult Disease Prevention Begins With Reducing Early Toxic Stress. Policies and practices intended to focus on health promotion and disease prevention might be strengthened considerably by greater attention to the potential effects of reducing toxic stress in early childhood. An increasing amount of research in neuroscience, social epidemiology, and the behavioral sciences, reviewed selectively in this article, suggests that a reduction in the number and severity of early adverse experiences will lead to a decrease in the prevalence of a wide range of health problems.

Building on this increasing body of evidence, the Centers for Disease Control and Prevention has proposed that child abuse and neglect be defined as a public health issue with lifelong consequences.[102] The implications of this emerging science for clinical practice are compelling. On the positive side, the primary care setting is arguably the most appropriate venue for a more proactive approach to the early identification and mitigation of potential causes of toxic stress in young children, such as child maltreatment (7.5% of children aged 2-5 years[103]), postpartum depression (13% of new mothers[104]), and parental substance abuse (9.8% of households with children aged <5 years[105]). Yet the challenges facing clinicians are formidable, including insufficient training and reimbursement to address complex social problems and limited access to specialized intervention services.[106] Nevertheless, the relatively high prevalence of early childhood trauma across all income groups underscores the need for greater attention, in both medical education and primary care practice, to its potential effects on lifelong health.

Early Childhood Programs Benefit Lifelong Health, Not Just Education. High-quality early childhood programs designed to produce positive effects on educational achievement and later workforce participation offer an important, unrecognized infrastructure for addressing the stress-related roots of social class disparities in health. Cost-benefit assessments of effective early childhood intervention for low-income children have documented significant financial returns to society through greater economic productivity, decreased welfare dependence, and lower rates of incarceration.[107-109] The degree to which en-

hanced efforts to reduce toxic stress might also reduce the prevalence of lifelong disease and reduce later health care costs also deserves careful consideration. To this end, the increasing gap between advances in evidence-based treatments for mental health impairments and the limited availability of services for those in need is highly problematic, particularly in the early childhood years. When early childhood program staff are not trained to address disruptive behaviors nor assisted in securing appropriate treatment for children or parents with serious mental health problems, opportunities for preventive intervention are missed and many troubled children are expelled from programs before they are given a chance to succeed.[110] Strengthening the capacity to address stress-related problems within the context of existing early care and education programs is likely to augment their effects.

Child Welfare Services: Missed Opportunity for Health Promotion. Publicly mandated services to protect children who have been abused or neglected present a particularly compelling and underused approach for addressing the immediate and long-term consequences of severe stress in early childhood. Since their establishment more than a century ago, child welfare services have focused exclusively on issues related to physical safety, reduction of repeated injury, and child custody. Advances in neuroscience now indicate that evaluations of maltreated children that rely exclusively on physical examination and radiographic screening are insufficient and must be augmented by comprehensive developmental assessments and the provision of appropriate intervention by skilled professionals as indicated.

A public infrastructure already exists to provide these additional services for children younger than 3 years through regularized referrals from child protective services agencies (which are mandated in each state) to early intervention programs for children with developmental delays or disabilities (which are available in all states under a federal entitlement). The most recent reauthorizations of the relevant federal legislation for both systems—the Keeping Children and Families Safe Act and the Individuals With Disabilities Education Act—include requirements for establishing such linkages, but their implementation has been limited. Greater public understanding of the effects of early abuse and neglect on lifelong health could help build support for more informed policy and practice.

Summary and Future Directions

An increasingly persuasive amount of research is emerging that supports the thoughtful construction of a new framework for health promotion and disease prevention. This model is based on mounting evidence that the origins of many adult diseases can be found among adversities in the early years of life that establish biological "memories" that weaken physiological systems and produce latent vulnerabilities to problems that emerge well into the later adult years.

The scientific concepts embedded in this framework are deeply grounded in the principles of evolutionary biology. Beginning as early as the first weeks after conception and continuing into early infancy, the immature "organism" "reads" key characteristics of its environment and prepares to adapt to an external world that can vary dramatically in its levels of safety, sufficiency, and peril. When early experiences prepare a developing child for conditions involving a high level of stress or instability, the body's systems retain that initial programming and put the stress response system on a short-fuse and high-alert status. Under such circumstances, the benefits of short-term survival may come at a significant cost to longer-term health.

Beyond its promising policy implications, the association between early adversity and subsequent health, learning, and behavior presents a compelling research agenda. Much work remains to be done to elucidate the precise causal mechanisms that explain these linkages. The identification of biomarkers of toxic stress and its physiological consequences offers particular promise as a source of short- and medium-term measures to assess the mediators of outcomes that require decades to confirm. In a parallel fashion, the design and implementation of new approaches to both the prevention and treatment of toxic stress and its consequences, beginning in the early childhood years, must be another key priority. For example, testing new community-based interventions or clinical treatments for preschoolers who have been abused or seriously neglected ought to be at least as high a research priority as conducting clinical trials of statins for school-aged children with elevated cholesterol levels. Focusing on access problems and differential treatment in the health care system is certainly important, but confronting the early childhood origins of disparities in physical and mental health may offer far greater return on investment.

In 2000, the Institute of Medicine and National Research Council released a report that synthesized existing knowledge about the effects of early experience on child development, including its underlying neurobiology.[14] Over the ensuing decade, public support for early childhood investment has increased substantially, with state expenditures for home visiting programs in the United States increasing from $13 million[111] to $280 million[112] and state pre-K from $1.6 billion[113] to $4.5 billion.[112] Much of the impetus behind this expanded investment comes from an increasing evidence base that demonstrates the extent to which effective interventions early in life can produce measurable benefits in later educational achievement, economic productivity, and responsible citizenship.[114] Advances in neuroscience and the biology of stress provide a compelling rationale for considering the inclusion of health promotion and disease prevention as a fully integrated part of that agenda.

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