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Home Visiting and the Biology of Toxic Stress: Opportunities to Address Early Childhood Adversity

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KEY WORDS

childhood adversity, toxic stress, life course, parental support, home visiting

ABBREVIATIONS

ACE—adverse childhood experiences

SE—social-emotional

PTSD—post-traumatic stress disorder

COPD—chronic obstructive pulmonary disease

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abstract

Home visiting is an important mechanism for minimizing the lifelong effects of early childhood adversity. To do so, it must be informed by the biology of early brain and child development. Advances in neuroscience, epigenetics, and the physiology of stress are revealing the biological mechanisms underlying well-established associations between early childhood adversity and suboptimal life-course trajectories. Left unchecked, mediators of physiologic stress become toxic, alter both genome and brain, and lead to a vicious cycle of chronic stress. This so-called “toxic stress” results a wide array of behavioral attempts to blunt the stress response, a process known as “behavioral allostasis.” Although behaviors like smoking, overeating, promiscuity, and substance abuse decrease stress transiently, over time they become maladaptive and result in the unhealthy lifestyles and noncommunicable diseases that are the leading causes of morbidity and mortality. The biology of toxic stress and the concept of behavioral allostasis shed new light on the developmental origins of lifelong disease and highlight opportunities for early intervention and prevention. Future efforts to minimize the effects of childhood adversity should focus on expanding the capacity of caregivers and communities to promote (1) the safe, stable, and nurturing relationships that buffer toxic stress, and (2) the rudimentary but foundational social-emotional, language, and cognitive skills needed to develop healthy, adaptive coping skills. Building these critical caregiver and community capacities will require a public health approach with unprecedented levels of collaboration and coordination between the healthcare, childcare, early education, early intervention, and home visiting sectors. *Pediatrics* 2013;132:S65–S73

INTRODUCTION

Childhood adversity plays a prominent role in influencing a child's development and eventual life course.¹⁻³ A wide array of adverse experiences in childhood has been associated with poor outcomes as diverse as depression, substance abuse, teenage pregnancy, incarceration, emphysema, obesity, type II diabetes, and cardiovascular disease.⁴⁻⁶ Only recently, however, have advances in the neurosciences, epigenetics, and the physiology of stress begun to reveal the biological mechanisms that underlie these well-established associations.^{3,7-9} This article will briefly review the epidemiologic associations between childhood adversity and unhealthy life-course trajectories before defining toxic stress and discussing its impact on brain development. By conceptualizing early childhood adversity in a broad and inclusive sense, and then linking it to the physiology of toxic stress, this article will highlight opportunities for caregivers and communities to intentionally and proactively build the early relationships and adaptive skills that minimize the long-term consequences of early childhood adversity.

CHILDHOOD ADVERSITY AND LIFE-COURSE TRAJECTORIES

Although the concept of adversity is self-evident, actually defining and measuring adversity is more problematic. Is the source of childhood adversity primarily at the child or individual level and owing to traumatic experiences, delays in development, disabilities, chronic diseases, temperaments, or other unusual physical or personal traits? Or is adversity attributable to parental or societal issues like poverty, divorce/single parenting, poor housing, lack of access to medical or mental health care, or the threat of violence or terrorism? Or, more likely, is it owing to a combination of both? To make matters worse,

adversity appears to be somewhat subjective, in that some children might have horrific experiences (eg, witnessing interpersonal violence) yet do very well, whereas other children might have long-lasting physiologic and behavioral changes owing to relatively minor trauma (like seeing a growling dog or falling off a bike).

Despite this individual variability, numerous epidemiologic studies have demonstrated a clear association between various forms of childhood adversity and multiple markers of poor physical and mental health as an adult. The Adverse Childhood Experiences (ACE) Study looked at over 17 000 middle class, middle-aged Americans (average age in the 50s) and found dose-dependent associations between the number of adverse childhood experiences (see Table 1) and a wide array of outcomes, including markers for social functioning, sexual health, mental health, risk factors for common diseases, and prevalent diseases (see Table 2).^{4,6} The retrospective ACE Study and several smaller but prospective studies indicate that adverse experiences in childhood influence behavior, mental wellness, and physical health decades later.^{1,2,5,10}

Because these epidemiologic studies are descriptive, no causal mechanisms

can be asserted. However, interventional studies like the Perry Preschool Project,¹¹ the Abecedarian Project,^{12,13} the Chicago Longitudinal Study,¹⁴ the Nurse Family Partnership,^{15,16} and others¹⁷ have demonstrated that alterations in a child's developmental milieu have profound and enduring effects on behavior and health decades later, suggesting that early childhood experiences do alter life trajectories in a meaningful way. Although econometric analyses of these early childhood interventions suggest a high return on investment, the salient features of these programs (child-centered vs family-centered vs community-centered) and the mechanisms underlying their success (promoting cognitive vs non-cognitive skills) remain a topic of debate.¹⁸⁻²⁰

MEASURING ADVERSITY: THE PHYSIOLOGIC STRESS RESPONSE

The subjective nature of adversity suggests that the metric of adversity cannot be the precipitants of stress (or the adverse experiences themselves), but rather the individual's physiologic response to those precipitants (the stress response). The physiologic mediators of stress (eg, cortisol, adrenaline) are quantifiable and can be measured both acutely (as stress

TABLE 1 Adverse Childhood Experiences Are Not Rare

	Women (n = 9367)	Men (n = 7970)	Total (n = 17 337)
Abuse			
Emotional	13.1	7.6	10.6
Physical	27.0	29.9	28.3
Sexual	24.7	16.0	20.7
Household dysfunction			
Mother treated violently	13.7	11.5	12.7
Household substance abuse	29.5	23.8	26.9
Household mental illness	23.3	14.8	19.4
Parental separation or divorce	24.5	21.8	23.3
Incarcerated household member	5.2	4.1	4.7
Neglect ^a			
Emotional	16.7	12.4	14.8
Physical	9.2	10.7	9.9

The Adverse Childhood Experiences (ACEs) Study asked over 17 000 middle class adults to recall if they had experienced any of these 10 ACEs before age 18 years. The prevalence of each ACE is given for both women and men. To determine an individual's ACE score, 1 point was given for each type of ACE recalled (for a maximum score of 10). Only 36% of the participants had an ACE score of 0, and 1 in 8 had an ACE score of 4 or more. All data are presented as percentages.

^a Wave 2 data only (n = 8667). Data from www.cdc.gov/ace/prevalence.

TABLE 2 Adverse Childhood Experiences Are Associated With Numerous Measures of Poor Health

I. Social Functioning
a. High perceived stress
b. Relationship problems
c. Married to an alcoholic
d. Difficulty with job
II. Mental Health
a. Anxiety
b. Depression
c. Poor anger control
d. Panic reactions
e. Sleep disturbances
f. Memory disturbances
g. Hallucinations
III. Sexual Health
a. Age of first intercourse
b. Unintended pregnancy
c. Teen pregnancy
d. Teen paternity
e. Fetal death
f. Sexual dissatisfaction
IV. Risk Factors for Common Diseases
a. Obesity
b. Promiscuity
c. Alcoholism
d. Smoking
e. Illicit drugs
f. IV drugs
g. High perceived risk of HIV
h. Multiple somatic symptoms
V. Prevalent Diseases
a. Ischemic heart disease
b. Chronic lung disease
c. Liver disease
d. Cancer
e. Skeletal fractures
f. Sexually transmitted infections

All of these adolescent and adult outcomes are associated with ACE scores in a dose-dependent and statistically significant manner. The higher the ACE score, the higher the risk for these measures of poor health. Adapted from www.cdc.gov/ace/findings and reference 4.

reactivity, or the magnitude of an acute stress response) or chronically (as elevated basal levels). Boyce et al have looked at stress reactivity in children and have shown that a high degree of variability exists.²¹ Traditionally, genetic predispositions were thought to play a major role in determining stress reactivity, but more recent data suggest that previous experiences also play an important role.²² Stress reactivity, much like brain development itself, results from a complex, dynamic interaction between genes (nature) and the environment (nurture) over

time. Neural pathways activated in response to frequent environmental stimuli are strengthened over time. Frequent, strong, or prolonged stress responses early in life are thus able to “set” a relatively lower threshold for future stress responses and to promote a high degree of stress reactivity.²³ So although stress reactivity may be genetically predisposed, it is nonetheless shaped by early individual experiences as well. This individual variability in stress reactivity might explain, at least in part, the varied responses to adversity. In sum, it may not be adversity itself that matters as much as the type of stress response that it provokes.

ADVERSITY AND STRESS ARE NOT ALWAYS NEGATIVE

High stress reactivity, however, is not always a negative trait or one that invariably leads to maladaptive behavioral responses. In the context of low adversity, children who have a high reactivity to stress are actually more social and successful academically than their peers who have a low reactivity to stress.²¹ However, in the context of high adversity, children who have high reactivity to stress fair worse than their peers who have low reactivity to stress.²¹ Hence, the consequences of high stress reactivity are contextual, with high reactivity promoting adaptive responses in the context of low adversity, but maladaptive responses in the context of high adversity. The relationship between adversity and stress is therefore complex. Adversity can promote stress reactivity, but stress reactivity can be beneficial in the context of low adversity.

In an attempt to refine this complex relationship between adversity and stress, the National Scientific Council on the Developing Child has proposed the following taxonomy of stress (also see Fig 1).²⁴ Positive stress is infrequent, mild, or brief and is characterized by

strong social-emotional (SE) supports. These strong SE supports allow the child to return to baseline relatively quickly and minimize the child's exposure to the physiologic mediators of stress (like cortisol and adrenaline). Examples of adverse experiences that could trigger a positive stress response (and the SE supports needed to buffer that stress) include a toddler's tumble or fall (under the reassuring eyes of a caregiver), a child's anxiety over beginning kindergarten or daycare (and an invested parent's firm but sympathetic response), or the adolescent's fear of failure on a long-term school project (that is overcome by a parent's assistance in simply learning how to organize or manage time). SE supports effectively buffer the potentially toxic consequences of prolonged exposure to the physiologic mediators of stress. More importantly, strong SE supports model effective social interactions and promote emotional regulation in the face of adversity, thereby building resilience.

Tolerable stress, on the other hand, does not necessarily build resilience, but sufficient levels of SE supports ensure that the child's physiologic stress response returns to baseline despite precipitants that are more frequent, intense, or sustained. Precipitants of tolerable stress include the death of a parent, divorce, or a natural disaster. Although tolerable stress and its precipitants have the potential to become chronic or toxic, tolerable stress is distinguished by the presence of adequate SE supports by invested adults.

Conversely, toxic stress results from the frequent, strong, or prolonged activation of the body's stress-response system. With toxic stress, the SE supports are insufficient to return the child's stress system back to baseline. The 10 childhood adversities studied in the ACE Study (see Table 1) are examples of potential precipitants of a toxic stress response. When SE experiences are not

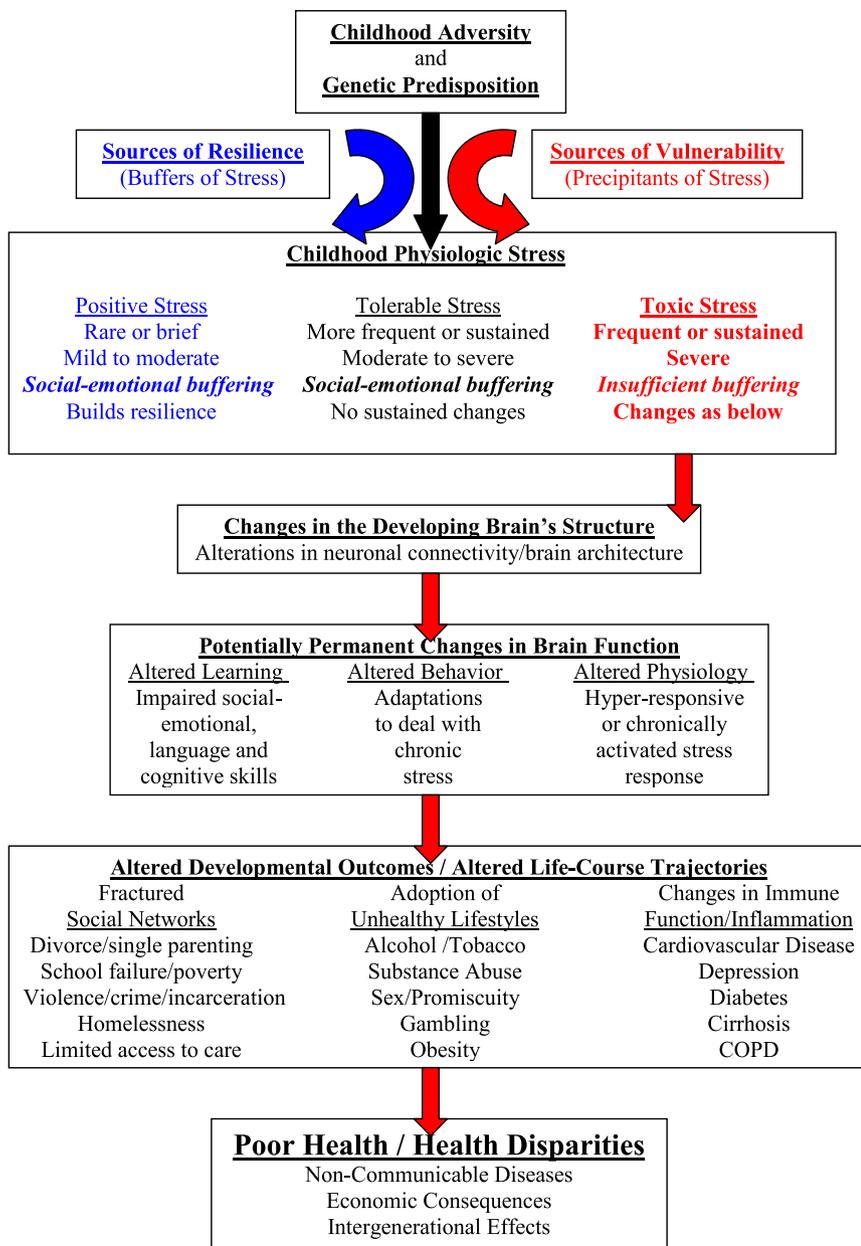


FIGURE 1

Toxic stress in childhood links adversity with poor health and health disparities. Adverse childhood experiences and genetic predispositions regarding stress reactivity interact to determine the type of childhood stress. Sources of resilience (strong SE supports; advanced SE, language and cognitive skills; previous adaptive behaviors to successfully overcome adversity) buffer this stress, whereas sources of vulnerability (poor SE supports; delays in development; harsh or abusive parenting; previous maladaptive behaviors in response to adversity) precipitate even more stress. Positive stress is rare or brief, mild to moderate in intensity, and builds resilience owing to appropriate levels of SE buffering by invested, caring adults. Tolerable stress is more frequent or sustained, moderate to severe in intensity, and has the potential to alter life courses, but does not, owing to adequate levels of SE buffering. Toxic stress is frequent, sustained, and severe in intensity, but is distinguished by the lack of sufficient levels of SE buffering. As a consequence, the physiologic mediators of stress (like cortisol and adrenaline) become “toxic” to the developing brain and alter the architecture and connectivity of the amygdala, hippocampus, and prefrontal cortex. These changes in brain structure may also alter critical brain functions such as stress regulation, learning, and executive functions like the adoption of healthy coping behaviors. The resulting changes in physiology, behavior, and social functioning are in turn associated with many of the adolescent and adult outcomes seen in the ACE study (Table 2). Collectively these maladaptive developmental outcomes lead to noncommunicable diseases, poor economic productivity, and the intergenerational propagation of health disparities.

supportive or nurturing (eg, a caregiver’s use of corporal punishment or verbal abuse), they are unable to buffer stress or to promote a return to baseline. Non-nurturing SE experiences may actually become sources of vulnerability, whereas nurturing SE experiences are important sources of resilience. In sum, the relationship between adversity and stress is both complicated and dynamic. The type of stress response precipitated by adversity is influenced by (1) the nature of the adversity, (2) the individual’s stress reactivity (which in turn is influenced by genetic predispositions and previous experiences), and (3) the level of SE supports (are SE experiences nurturing and building resilience, or are they non-nurturing and generating additional vulnerabilities?).

BRAIN DEVELOPMENT AND TOXIC STRESS

Advances in neuroscience have revealed that the process of brain development is driven by a dynamic interaction between the genome (nature) and the environment (nurture).²⁵ Epigenetic mechanisms like DNA methylation and histone acetylation are able to transduce experiences with the environment into long-lasting, even intergenerational changes in gene expression.^{26–35} So although the inherited genetic program is thought to provide a general blueprint for brain architecture, the environment is able to influence which genes are used, when they are used during the course of development, and where they are used within the developing brain. In short, environmental experiences, and the neuronal activity that they generate, literally sculpt brain architecture and neuronal connectivity.

To understand the impact of adverse experiences on the developing brain, begin by looking at where the physiologic mediators of toxic stress are acting. Glucocorticoid receptors are expressed in high levels in 3 prominent

brain structures: the amygdala, the hippocampus, and the prefrontal cortex.^{36–39} The amygdala is part of the limbic system, is activated during stress, and is thought to play an important role in generating impulsive or aggressive behaviors. The fact that the amygdala is enlarged and more reactive in patients who have post-traumatic stress disorder (PTSD) or significant childhood adversity reinforces the notion that the neuronal pathways underlying the stress response (like those in the amygdala) are built-up, reinforced, and strengthened by adverse experiences, leading to a hyper-responsive or chronically active stress response (ie, toxic stress).^{40–43}

Another example of how toxic stress alters brain architecture is seen in the hippocampus.^{38,39} Although neuronal proliferation was once thought to occur only prenatally, new neurons are continuously being generated in the adult hippocampus, and these new neurons are known to play an important role in learning and the formation of new memories.⁴⁴ In animal studies, chronic stress decreases this neuronal proliferation and results in impaired learning.^{45,46} Recent MRI data suggest that decreased hippocampal neurogenesis may well play a role in patients who have PTSD, as they have selective volume losses in specific hippocampal areas known to be important for learning.^{47,48} Although acute deficits in learning and memory might be an evolutionarily advantageous “protective” mechanism that allows individuals to “get over” very traumatic experiences, chronic or ongoing impairments in learning might also delay the development of critical SE, language, and cognitive skills. The hippocampus also highlights the importance of SE buffering, as supportive parenting in early childhood is associated with increased hippocampal volumes in middle childhood.⁴⁹

One final example is the prefrontal cortex, which is thought to play an

important role in regulating behavior by suppressing impulses and emotions arising from the amygdala and other parts of the limbic system.^{50–52} In animal studies, exposure to chronic stress or glucocorticoids alters the synaptic connectivity within the prefrontal cortex,^{52,53} and this may limit the ability of the prefrontal cortex to (1) suppress the impulsivity and aggression of the limbic system, and (2) execute adaptive responses (rather than maladaptive responses) to stress.^{54–56} Stress-induced changes in brain structure parallel the well-described impact of significant childhood adversity on a variety of brain functions, including the modulation of physiologic responses (hyper-responsive or chronically active stress response), learning (impaired memory), and the regulation of behavior (the ability to execute adaptive vs maladaptive responses to stress).^{3,39,57}

These toxic stress-induced changes in brain structure and function mediate, at least in part, the well-described relationship between adversity and altered life-course trajectories (see Fig 1).^{4,6} A hyper-responsive or chronically activated stress response contributes to the inflammation and changes in immune function that are seen in those chronic, noncommunicable diseases often associated with childhood adversity, like chronic obstructive pulmonary disease (COPD), cirrhosis, type II diabetes, depression, and cardiovascular disease.^{4,6} Impairments in critical SE, language, and cognitive skills contribute to the fractured social networks often associated with childhood adversity, like school failure, poverty, divorce, homelessness, violence, and limited access to healthcare.^{4,19,58–60} Finally, behavioral allostasis, or the adoption of potentially maladaptive behaviors to deal or cope with chronic stress, begins to explain the association between childhood adversity and unhealthy lifestyles, like alcohol, tobacco, and substance

abuse, promiscuity, gambling, and obesity.^{4,6,61} Taken together, these 3 general classes of altered developmental outcomes (unhealthy lifestyles, fractured social networks, and changes in immune function) contribute to the development of noncommunicable diseases and encompass many of the morbidities associated epidemiologically with childhood adversity.^{4,6}

HOME VISITING AND OPPORTUNITIES FOR EARLY INTERVENTION AND PREVENTION

The noncommunicable diseases associated with early childhood adversity have garnered a great deal of attention recently, as they are predicted to account for 90% of the morbidity seen in high-income countries by the year 2030.⁶² Although this has prompted some to focus on the automatic brain processes that perpetuate the associated unhealthy lifestyles,⁶³ relatively little attention has been given to preventing or mitigating the toxic stress that allows these automatic processes and unhealthy behaviors to be learned and adopted in the first place.

Understanding the role that toxic stress and behavioral allostasis play in mediating the lifelong consequences of childhood adversity highlights important opportunities for early intervention and prevention (see Fig 2). Although ongoing advocacy efforts to address childhood adversity and to prevent the potential precipitants of toxic stress responses are certainly warranted, so are efforts to improve the capacity of caregivers and communities to promote the safe, stable, and nurturing relationships that assist in turning off the child's physiologic stress in response to adversity.^{59,64} However, preliminary data indicate that the level of adversity and risk factors in mothers participating in home visiting programs is very high (oral communication between C. Blodgett

and co-guest editors, June 2013). In fact, anecdotal evidence from local home visiting programs in Washington state suggests that high levels of recent adversity and distress are the “new normal” for home visiting. If this maternal adversity and distress impairs the mother’s ability to form a safe, stable, and nurturing relationship with her child, the maternal adversity puts the child at risk for toxic stress. Home visiting with well-trained specialists is an important opportunity to support the capacity of mothers to develop strong, responsive early relationships with their children. The SE buffering afforded by these critical early relationships prevents adversity from becoming toxic. One important objective, then, is for pediatricians, early educators, and early intervention and home visiting specialists to collaboratively increase the capacity

of parents, caregivers, and communities to nurture those critical first relationships that buffer toxic stress and build a sturdy foundation for future learning, behavior, and health.^{59,64,65}

Similarly, ongoing efforts to “unlearn” unhealthy lifestyles and to treat noncommunicable diseases are warranted,⁶³ but so are efforts to improve the capacity of caregivers and communities to encourage and proactively build the rudimentary but foundational SE, language, and cognitive skills that allow for the adoption of healthy, adaptive coping skills.^{18,20,66,67} Ultimately the prevention of all childhood adversity is an unrealistic objective and, to a certain extent, an undesirable one. Positive stress is not the absence of adversity, but it results from adversity that is dealt with in a healthy, adaptive manner, thereby building confidence and resilience for

the future. This challenges the pediatric, home visiting, and early intervention communities to intentionally and proactively build skills, rather than waiting and screening for delays before intervening. The idea that parents and caregivers might proactively build the rudiments of resilience is not without precedent.^{67,68} Vygotsky suggested that the role of parents, caregivers, and teachers is to work within the child’s zone of proximal development so the child will learn to master skills that were previously beyond their independent ability.⁶⁹ This is the theory behind both Reach Out and Read^{70,71} and more recent efforts to decrease obesity by nurturing the foundational motor skills needed for an active lifestyle.^{72–74} The current challenge, then, is for pediatricians, home visitors, and early educators to collaboratively increase the capacity of caregivers and communities to nurture those rudimentary but foundational SE, language, and cognitive skills as they emerge developmentally. Home visiting with well-trained specialists is an important opportunity to build the capacity of mothers to support the child’s social, emotional, and cognitive development within the natural environment of the home.

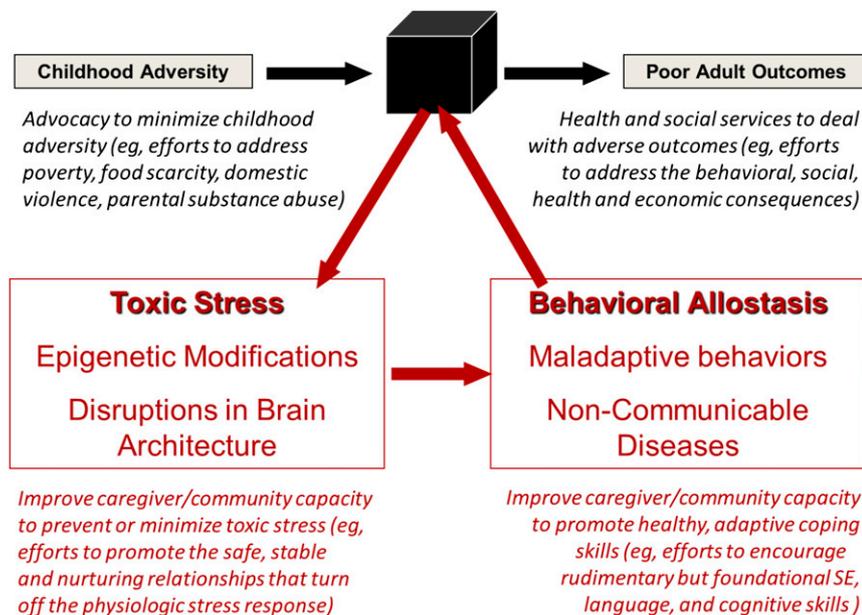


FIGURE 2 Opportunities for minimizing the lifelong effects of early childhood adversity. Without an understanding of the biological mechanisms underlying the well-established associations between childhood adversity and poor adult outcomes (the proverbial black box), interventions (examples are in *italics*) are largely limited to preventing childhood adversity (*through advocacy*) and to addressing the long-term behavioral social, health, and economic consequences (*through health and social services*). Because toxic stress and behavioral allostasis underlie these well-established associations, important opportunities exist to minimize the impact of child adversity by *promoting the safe, stable, and nurturing relationships that buffer toxic stress, and encouraging the rudimentary but foundational SE, language, and cognitive skills that promote resilience and the adoption of healthy, adaptive coping skills*. Home visiting is a mechanism to capitalize on these early opportunities within the natural environment of the home.

SUMMARY AND IMPLICATIONS FOR HOME VISITING IN THE FUTURE

Framing childhood adversity in the context of the physiologic stress response begins to explain the strong associations between adverse experiences in childhood and a wide array of altered developmental outcomes and life-course trajectories. Because “toxic stress” and “behavioral allostasis” underlie these well-established associations, important opportunities exist to minimize the impact of child adversity by intervening early to prevent toxic stress and to proactively build the rudiments of resilience. Home visits are an important mechanism for improving

the capacity of caregivers to (1) promote the safe, stable, and nurturing relationships that buffer toxic stress, and (2) encourage the rudimentary but foundational SE, language, and cognitive skills that promote resilience and the adoption of healthy, adaptive coping skills.

That said, building these critical caregiver capacities will require a well-trained workforce of home visiting specialists who are adept at addressing child-, family-, and community-level barriers. Ideally these specialists would also be prepared to play an integral role

in collecting noninvasive biomarkers (eg, salivary cortisol samples) to further stratify risk and eventually assess the efficacy of specific interventions for specific populations. Strengthening the effectiveness of home visiting and building a research infrastructure are likely to be 2 key components of the home visiting research agenda (Home Visiting Research Agenda, by the Home Visiting Research Network, draft for public comment, available June 17, 2013 at www.hvrn.org/read-and-comment).

Home visiting specialists, much like pediatric medical homes, cannot address

early childhood adversity and toxic stress in isolation. However, both are integral elements of a desperately needed public health approach to prevent the intergenerational transfer of toxic stress and disparities in health, education, and economic productivity. Building the community capacities to support such a public health approach to toxic stress will require unprecedented levels of collaboration and coordination between the health-care, childcare, early education, early intervention, and home visiting sectors.

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