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ADVANCES IN PEDIATRICS

Toxic Stress in Children and Adolescents

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Keywords

• Toxic stress • Stress • Adverse childhood experiences • Adversity • Multisystemic alterations • Chronic disease • Child health • Adolescent health

Key points

- Early life adversity, also referred to as adverse childhood experiences (ACEs), includes stressful or traumatic experiences in childhood and abuse, neglect, and household dysfunction.
- ACEs put children at risk of negative physical, mental, and behavioral health outcomes.
- When a child is exposed to stressors, such as early life adversity, the body's natural stress response can become maladaptive or toxic to the body.
- The toxic stress response results from a disruption of the circuitry between neuroendocrine and immune systems, and it affects multiple biological systems, laying the foundation for long-term health outcomes.

INTRODUCTION

Advances in science have provided evidence of the complex relationship between the social environment, child development, and long-term health outcomes. The medical field, and pediatrics in particular, has become increasingly involved in addressing these complex relationships [1]. Early childhood and adolescence are known to be sensitive periods of development during which biological systems are readily shaped by both positive and negative external influences and experiences [2,3]. Exposure to frequent, prolonged, or intensely negative experiences in childhood (ie, early life adversity) has been associated with long-term negative health outcomes, including ischemic heart disease, cancer, diabetes, asthma, and premature death, among others [1,4–8].

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Investigating the precise biological mechanisms underlying the association between exposure to early life adversity and negative health outcomes is an important emerging field of biomedical research. The current body of data suggests that a maladaptive response to stress during childhood, referred to as a toxic stress response, plays an important role in the pathway from early adversity to disease.

In this article, the authors describe early life adversity and toxic stress, and their implications for pediatric health.

- First, early life adversity and health outcomes are described, including definitions of early life adversity and its prevalence, and associations found between these early experiences and long-term health outcomes.
- Then toxic stress is defined, as part of a continuum of the physiologic stress response and as an important biological pathway linking early life adversity to negative health outcomes. The authors provide an overview of the core anatomic and functional components of the stress response as a foundation for understanding the maladaptive response characteristic of toxic stress. Also presented is evidence of how prolonged exposure to severe or frequent adversity in early life can have an effect on the neuroendocrine immune circuitry that ultimately alters the organism's ability to cease the stress response.
- Finally, the pathogenesis of the toxic stress response is addressed as well as its impact on multiple organ systems, and the risk of negative health outcomes.

EARLY LIFE ADVERSITY AND HEALTH OUTCOMES

Stressful or traumatic events experienced in childhood or adolescence are referred to by many terms, including early life adversity, early life stress, early life trauma, or adverse childhood experiences (ACEs).

In mental and behavioral health, there is an extensive history of studying associations between negative early life experiences and mental and behavioral health outcomes; the Adverse Childhood Experience Study (ACE Study), however, was among the first linking early life adversity and long-term physical health outcomes in a large sample [9]. The categories of adversity used in the ACE Study represent a limited set of risk factors which, although not exhaustive, have become commonly cited as defining categories of adversity in research associating childhood adversity and physical health outcomes. Table 1 exhibits the 3 categories of adversity and definitions used in the ACE Study.

The ACE Study was conducted between 1995 and 1997 at the Kaiser Permanente's Health Appraisal Clinic in San Diego, in collaboration with the Centers for Disease Control and Prevention [9]. The study assessed the associations between ACEs and physical, behavioral, and mental health outcomes. Medical history and data on exposure to ACEs were collected in 2 waves from 18,175 patients of the San Diego clinic (68% overall response rate) [5,9].

In the first wave of the ACE Study, patients were assessed on 2 categories of adversity: abuse and household dysfunction [9]. In the second wave, items on neglect were added [10]. Additional traumatic or stressful experiences with evidence of long-term health impacts include exposure to community violence

Table 1
A adverse childhood experiences, by category

ACE category	Definition
Abuse	• Psychological *Did a parent or other adult in the household …* ○ Often or very often swear at, insult, or put you down? ○ Often or very often act in a way that made you afraid that you would be physically hurt? • Physical *Did a parent or other adult in the household …* ○ Often or very often push, grab, shove, or slap you? ○ Often or very often hit you so hard that you had marks or were injured? • Sexual *Did an adult or person at least 5 years older ever …* ○ Touch or fondle you in a sexual way? ○ Have you touch their body in a sexual way? ○ Attempt oral, anal, or vaginal intercourse with you? ○ Actually have oral, anal, or vaginal intercourse with you?
Neglect	• Emotional *Did you often or very often feel that …* ○ No one in your family loved you or thought you were important or special? ○ Your family didn't look out for each other, feel close to each other, or support each other? • Physical *Did you often or very often feel that …* ○ You didn't have enough to eat, had to wear dirty clothes, and had no one to protect you? ○ Your parents were too drunk or high to take care of you or take you to the doctor if you needed it?
Household dysfunction	• Divorce or separation ○ Were your parents ever separated or divorced? • Mother treated violently *Was your mother (or stepmother) …* ○ Often or very often pushed, grabbed, slapped, or had something thrown at her? ○ Sometimes, often, or very often kicked, bitten, hit with a fist, or hit with something hard? ○ Ever repeatedly hit over at least a few minutes or threatened with, or hurt by, a gun or knife? • Substance abuse ○ Did you live with anyone who was a problem drinker or alcoholic or anyone who used street drugs? • Mental illness ○ Was a household member depressed or mentally ill or attempt suicide? • Criminal behavior in household ○ Did a household member go to prison?

Adapted from Adverse Childhood Experiences Study. Finding your ACE score. Available at: http://www.acestudy.org/yahoo_site_admin/assets/docs/ACE_Calculator-English.127143712.pdf. Accessed May 2, 2016.

[11,12], bullying [13], homelessness [14], parental stress [15], economic hardship [16], and discrimination [17].

Prevalence of early life adversity

Data from the ACE Study indicated that almost two-thirds (63.5%) of adults had at least one ACE, and 12% had 4 or more ACEs [4]. In a more recent, nationally representative sample across 10 states in the United States and the District of Columbia, using data from the Behavioral Risk Factor Surveillance Survey (BRFSS), Gilbert and colleagues [18] also found that approximately two-thirds of adults reported at least one early life adversity. The BRFSS is a cross-sectional population-based telephone survey of noninstitutionalized households. In the BRFSS, early life adversity is defined as abuse (sexual, physical, and emotional) and household dysfunction (having lived with parents/adults who separated/divorced, had a mental illness, abused alcohol, abused drugs, was incarcerated, or was involved in intimate partner violence) experienced before age 18 [18], which is similar to the definition used in the first wave of the ACE Study. Consistent with national data, results from a study using California BRFSS data from 2008, 2009, 2011, and 2013 showed that 61.7% of surveyed adults reported experiencing at least one ACE, and 16.7% reported having experienced 4 or more ACEs [19].

In children, nationally representative studies on ACEs have shown a prevalence of having experienced at least one early life adversity ranging from 33% to nearly 50% of the population [20–22]. Among 701 patients (median age = 7.33 years, SD = 5.47 years) receiving medical services at a community-based primary care clinic in San Francisco, 67.2% of participants had experienced one or more ACE (abuse, neglect, and household dysfunction) and 12% experienced 4 or more ACEs [23]. Among children at high risk for maltreatment, the percentage experiencing at least one early adversity was found to reach as high as 91% [24].

Health outcomes associated with early life adversity

Most studies on early life adversity and health outcomes have been adult retrospective reports of events experienced before age 18 and their adult health outcomes. These studies have been important in identifying associations between early adversity and health outcomes that generally take years to manifest into clinically relevant forms.

Data from the ACE Study suggest a dose-response relationship between the number of ACEs experienced by an individual and negative health outcomes. In comparison with reporting no ACEs, reporting 4 or more ACEs was associated with significantly increased odds of developing 6 of 10 leading causes of death in the United States after adjusting for age, gender, race, and educational attainment: ischemic heart disease (2.20), any cancer (1.90), stroke (2.40), chronic bronchitis or emphysema (3.90), diabetes (1.60), and attempted suicide (12.20) [9,25]. Fig. 1 shows the odds of disease and health risk behavior for those reporting 4 or more ACEs compared with those reporting zero ACEs.

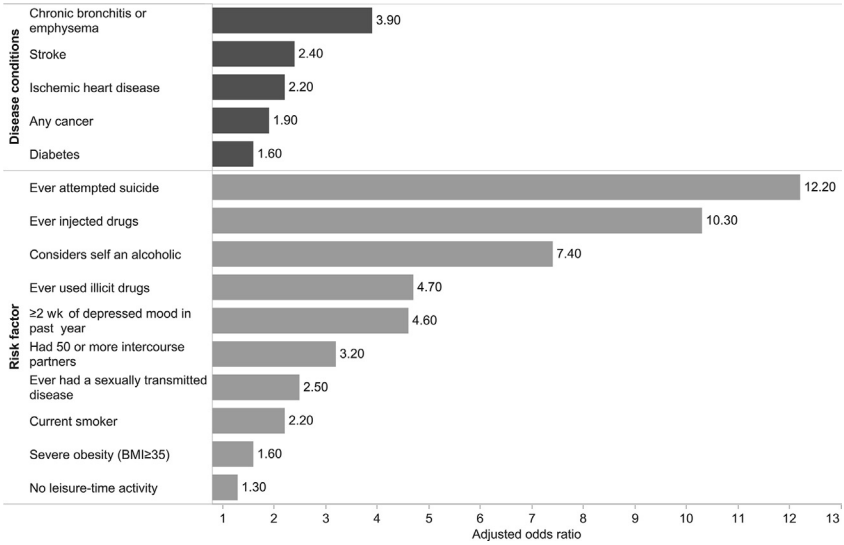


Fig. 1. Odds of outcomes among individuals experiencing 4 or more ACEs. ACEs, adverse childhood experiences; BMI, body mass index. Adjusted for age, gender, race and educational attainment. Referent group 0 ACEs. *Data from* [9]

Additional research on exposure to early life adversity with different populations, including children and adolescents, further supports the conclusion of a relationship between early life adversity and child and adult health outcomes. After 10 years of follow-up, Karlen and colleagues [26] found an association between early life adversity and an increased incidence of childhood illnesses including, dermatitis and eczema, acute upper respiratory illness, otitis media, and viral infections, among others. On the other end of the life span, Brown and colleagues [5] found that people with 6 or more ACEs died nearly 20 years earlier than did those with no ACEs (age 60.6 vs 79.1). Additional findings from various studies on early life adversity and mental, behavioral, and physical health outcomes are summarized in Table 2. In addition to these long-term health consequences, exposure to trauma in childhood has been associated with abnormal development, learning difficulties, and additional pediatric conditions, such as failure to thrive, enuresis, insomnia, and obesity [27].

EARLY LIFE ADVERSITY AND TOXIC STRESS

The etiologic pathways by which the effects of early life adversity becomes embedded in the body and brain of the developing child have yet to be fully understood, but promising research suggests that a dysregulation of the physiologic stress response plays a critical role in the development of negative health outcomes. Although influenced by genetic variability and social and biological protective factors, early life adversity appears to act on the organism as a stressor. Exposure to severe, frequent, and/or prolonged adversity, during

Table 2
Health outcomes associated with early adversity

Outcome	Adults	Children and adolescents
Mental/behavioral health	• Alcoholism • Anxiety • Bipolar disorder • Depression • Difficulty controlling anger • Hallucinations • High stress • Panic reactions • Posttraumatic stress disorder • Smoking • Substance abuse • Suicide	• Bullying • Dating violence • Delinquent behavior • Learning difficulties • Physical fighting • Weapon-carrying
Physical health	• Any cancer • Autoimmune disease • Cardiovascular disease • Chronic lung disease/chronic bronchitis or emphysema • Diabetes • Early death • Fair or poor self-rated health • General poor health • Headaches • Hepatitis or jaundice • Ischemic heart disease • Obesity • Sexual transmitted infections • Sleep disturbances • Skeletal fracture • Stroke	• Acute lower and upper respiratory infections • Adolescent pregnancy • Attention deficit hyperactivity disorder • Asthma • Autism • Conjunctivitis • Dermatitis and eczema • Illness requiring a doctor • Intestinal infectious disease • Lifetime asthma • Otitis media • Overweight or obese • Poor dental health • Poor general health • Pneumonia • Urinary tract infections • Urticaria • Viral infections of unspecified site

Data from Refs. [9,10,20–24,26,125–131].

sensitive periods of development without adequate protective factors in place (eg, supportive caregiving), can cause lasting changes to the stress response regulation. Therefore, toxic stress represents the maladaptive and chronically dysregulated stress response that occurs in relation to prolonged or severe early life adversity [28].

The stress response

The physiologic response to a stressor involves a complex interplay of contextual and biological factors, such as the intensity or severity of the stressor, individual genetic characteristics, gene-environment interactions, family environmental factors, and developmental experiences [29,30]. Protective factors, including biological and social resilience, are also involved in determining how the body responds to environmental stressors [28,29].

The spectrum of the stress response includes positive, tolerable, and toxic stress [1,28], as depicted in Fig. 2. The physiologic response to stress depends on the nature of the stressors and the availability of buffering and coping strategies. Although there is promising evidence from animal studies that the toxic stress response may be mitigated, the extent to which an individual's stress response can move along the continuum is currently unknown [28].

A positive or tolerable stress response is characterized by a return to homeostasis, whereas a toxic stress response may induce lasting changes to the organism. Toxic stress is characterized by prolonged or frequent activation of the stress response that leads to a dysregulation of the neuroendocrine immune circuitry, which produces altered levels of important hormones and neurotransmitters and ultimately changes in brain architecture and multiple organ systems. Because this maladaptive stress response occurs during sensitive periods of development, its effects can become incorporated into long-term regulatory physiologic processes, and subsequently, can increase vulnerability to developmental, biological, mental, and behavioral adverse outcomes, resulting in an increased risk for chronic diseases in adulthood [11].

Anatomy and physiology of the stress response

The stress response has both central and peripheral components. The central components of the stress response include the structures of the central nervous system (CNS): amygdala, hypothalamus, and parts of the brainstem (locus coeruleus in the pons; medulla). The peripheral components of the stress response include the sympatho-adrenomedullary (SAM) axis and the hypothalamic-pituitary-adrenal (HPA) axis. Fig. 3 summarizes the core anatomy of the SAM and HPA axes.

In response to a stressor, the SAM and HPA axes are both activated. The trigger stressor activates the amygdala, which has evolved to detect and signal environmental threats to survival [31]. Activation of the amygdala is modulated by central structures: the hippocampus (important for learning and memory), the prefrontal cortex (implicated in executive functions and cognition), and the locus coeruleus in the pons (responsible for mediating the autonomic effects during stress response) [32]. The complex interplay of the pathways involved in the stress response is highlighted in Fig. 3; key stress-induced hormones are summarized in Table 3.

Activation of the stress response

Sympatho-adrenomedullary axis activation. Once the stimulus is interpreted as a stressor, the SAM axis is activated, releasing catecholamines such as norepinephrine and epinephrine (also known as noradrenaline and adrenaline). The activation of the sympathetic nervous system has both central and peripheral nervous system modulators and operates through a series of interconnected neurons. The locus coeruleus activates the sympathetic neurons in the spinal cord, which are distributed to vessels, major organs, glands, and other parts of the body where they release norepinephrine. Sympathetic neurons also activate the secretion of epinephrine from the adrenal medulla.

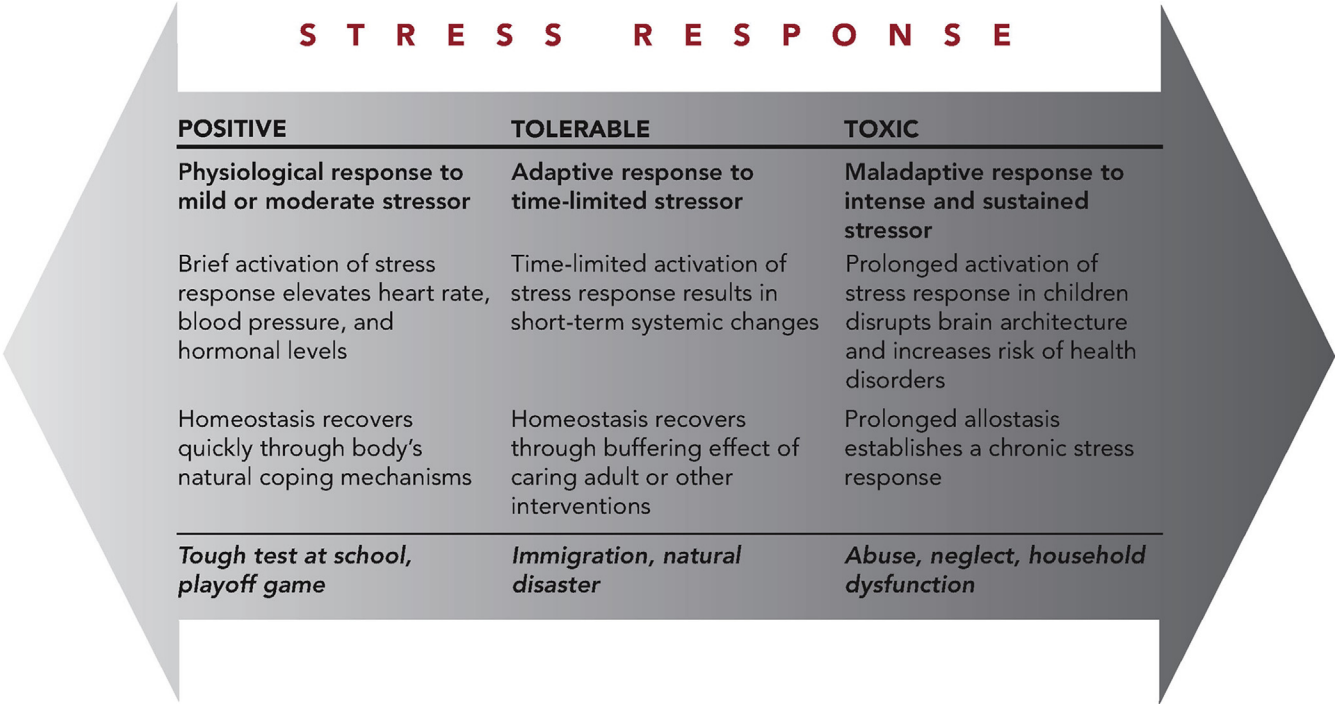
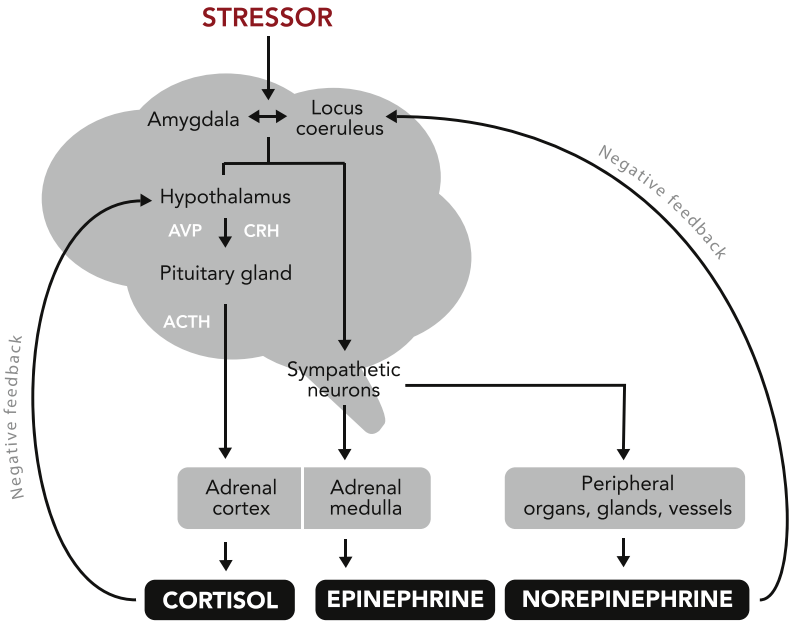


Fig. 2. Spectrum of the stress response: positive, tolerable, and toxic.



HPA axis

The HPA axis controls the body's response to stress and is a complex interplay of direct interactions. The HPA axis is composed of:

1. The **hypothalamus** which releases AVP and CRH to the pituitary gland
2. The **pituitary gland** which secretes ACTH when stimulated by AVP and CRH
3. The **adrenal cortex** which secretes glucocorticoids (cortisol) when stimulated by ACTH

SAM axis

The SAM axis mediates a rapid response to stress through interconnected neurons and regulates autonomic functions in multiple organ systems. The SAM axis is composed of:

1. The **sympathetic neurons** which release epinephrine and norepinephrine and activate the body's "fight or flight" response
2. The **parasympathetic neurons** which withdraw the activity of the sympathetic neurons and promote the body's "rest and digest" response
3. The **adrenal medulla** which when triggered by the sympathetic neurons secretes circulating epinephrine and activate the body's "fight or flight" response

Fig. 3. Stress response pathway. HPA axis, hypothalamic-pituitary-adrenal axis; SAM axis, sympathoadrenomedullary axis; AVP, arginine vasopressin; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropin hormone.

Circulating norepinephrine and epinephrine activate the fight-or-flight response to promote redirection and availability of blood, oxygen, and energy to vital organs, through the activation of simultaneous physiologic changes [33,34]. These changes can be described as follows:

- Blood circulation: Constriction of the blood vessels, and increase in the force of cardiac contraction to push blood to the brain, muscles, heart, and other vital

Table 3
Stress-induced hormones

Hormone	Source	Description
CRH	Hypothalamus	Principal regulator of the pituitary-adrenal axis: targets the anterior pituitary
AVP	Hypothalamus and posterior pituitary gland	Targets the anterior pituitary and regulates body's homeostasis
ACTH	Anterior pituitary gland	Targets the adrenal cortex to secrete ACTH
Norepinephrine	Sympathetic neurons in the brain stem (medulla and locus coeruleus)	Activates fight-or-flight response
Epinephrine	Adrenal medulla	Activates fight-or-flight response
Glucocorticoids	Adrenal cortex	Final effectors of the HPA axis. Cortisol is one of the most abundant human glucocorticoids

Abbreviations: ACTH, adrenocorticotropin hormone; AVP, arginine vasopressin; CRH, corticotropin-releasing hormone; HPA axis, hypothalamic-pituitary-adrenal axis.

organs. The effect of these changes is an increase in heart rate, blood pressure, muscle tone, and alertness.
- Respiration: Increase in the respiratory rate and dilation of the small airways in the lungs to increase the intake of oxygen being shunted to the brain and stressed organ systems, where it is most needed.
- Metabolism: Activation of an intermediate metabolic pathway (gluconeogenesis, lipolysis) in order to release stored glucose and fat to be used as an energy source.

Behavioral adaptive changes of the SAM axis activation include the following [35,36]:

- Increased arousal, alertness, and vigilance
- Improved cognition
- Focused attention
- Euphoria
- Enhanced analgesia
- Elevations in body temperature
- Inhibition of vegetative functions (eg, appetite, feeding, digestion, growth, reproduction, and immunity)

Finally, detoxification functions are activated to clear the organism of unnecessary metabolic and catabolic products [35,36].

Hypothalamic-pituitary-adrenal axis activation. In addition to activating the SAM axis in response to a stressor, the amygdala and the locus coeruleus also signal the hypothalamus, inducing activation of the HPA axis [37]. Activation of the HPA axis during exposure to stressors increases the release of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) from the hypothalamus to the pituitary gland. In turn, the pituitary gland

secretes adrenocorticotropin hormone (ACTH) into the bloodstream. ACTH targets the adrenal cortex, which secretes glucocorticoids. Glucocorticoids are the final effectors of the HPA axis, with cortisol (or hydrocortisone) being the most abundant of the human glucocorticoids [38].

Physiologically normal HPA axis function depends on the balanced activation of two corticosteroid receptors with opposing effects: mineralocorticoid and glucocorticoid receptors [36,39].

- Mineralocorticoid receptors are found in the hypothalamus and regulate blood pressure, the HPA axis circadian rhythm, cerebral glucose availability, and neuronal responsivity, making the organism ready if a fight-or-flight response is needed.
- Glucocorticoid receptors are found in the hypothalamus and anterior pituitary and play an important role in the termination of the stress response through negative feedback inhibition of the secretion of CRH and ACTH. This negative feedback loop serves to limit the duration of the total tissue exposure of the organism to glucocorticoids, minimizing the effects of these hormones on biological systems and shutting down the cascade of effects observed during the response to stress once the organism is no longer exposed to the stressor.

Central nervous system activation. The SAM and HPA axes also interact with other major components of the CNS:

- The reward center (mesocorticolimbic system) is important in cognition and motivation and is a target for substance abuse and drug addiction. This system is composed of dopaminergic neurons of the ventral tegmental area (VTA), involved in anticipatory phenomena and cognitive functions, and is widely implicated in the natural motivational, reinforcement, and reward circuitry of the brain. The VTA contains neurons that project to numerous areas of the brain, including the prefrontal cortex [40–42].
- The emotional center (amygdala-hippocampus complex) is important for memory, decision making, and emotional reactions (especially fear), and it mediates the retrieval and emotional analysis of relevant information of the stressor [40,43].
- The thermoregulatory center increases the core temperature and mediates the pyrogenic effects of proinflammatory cytokines, tumor necrosis factor-α, interleukin (IL)-1, and IL-6 [36].
- The appetite-satiety center in the hypothalamus regulates appetite in response to stress. Acute elevations in CRH concentrations can lead to loss of appetite and anorexia [44,45]. Fasting enhances CRH secretion [44], inhibits the sympathetic nervous system and activates the parasympathetic nervous system [45].

Once the individual is no longer exposed to the stressor, or is in the presence of a supportive caregiver and has effective coping mechanisms that help the body adapt to the stressor, the parasympathetic subdivision of the autonomic nervous system intervenes to withdraw the activation of the SAM axis, while cortisol regulates the activation of the HPA axis through negative feedback

inhibition of the secretion of CRH and ACTH [28]. In concert, these processes terminate the stress response and facilitate the return of the body to homeostasis.

Dysregulation of the stress response

The normal physiologic stress response is an adaptive and time-limited process to maintain the homeostasis necessary for survival [46]. Homeostasis is achieved through self-regulating properties that biological systems have in place to maintain the internal stability of key physiologic variables, such as body temperature and energy balance. As part of achieving homeostasis, the organism activates processes that are essential for successful adaptation to prevent an overresponse from both the central and the peripheral components of the stress response. These adaptive processes, known as allostasis, rely on the organism's ability to detect external and internal changes and to activate appropriate adaptive responses [47]. The time-limited nature of the stress response makes its systemic short-term changes tolerable and useful for the healthy development of the child's adaptive stress response [40]. Allostasis becomes adaptive for the organism in the context of coping with a stressful situation. Conversely if the exposure to the stressful situation is intense, chronic, or repeated and occurs during sensitive periods of development and without a buffering factor, it is associated with a prolonged or frequent and dysregulated activation of these allostatic processes [48–50] and can become maladaptive and, over time, toxic.

During a chronic (ie, toxic) stress response, the organism may become unable to regulate the SAM and HPA axes due to a disruption of negative feedback regulation. If the toxic stress response is not buffered, for example, by supporting caregiving and effective coping mechanisms, the organism may fail to regulate the stress response. This dysregulation can lead to a prolonged activation of the SAM and HPA axes and a dysregulation of the release of the stress-induced hormones (eg, cortisol) and catecholamines (eg, epinephrine and norepinephrine). As a result, the circulating stress-induced hormones and catecholamines may become chronically excessive or chronically deficient [35,36,39].

Biological alterations of the stress response

The toxic stress response is particularly concerning for children because the developing brain is highly plastic and influenced by the environment. The dysregulation of the stress response produces significant biological alterations that can damage brain architecture and impact the nervous, endocrine, and immune systems, which are highly integrated biological systems, often referred to as the neuroendocrine immune circuitry [51]. These systems interact reciprocally as the mediators of the toxic stress response. Prolonged or frequent activation of the stress response in early childhood reduces neuronal connections in important areas of the CNS that are key mediators and regulators of the SAM and HPA axes.

Individuals with altered functioning in the nervous, endocrine, and immune systems have been found to be at increased risk for developing chronic disorders [38]. Moreover, epigenetic modifications in childhood play a role in damaging the systems involved in the future response to adversity in adulthood.

Nervous system

In the nervous system, prolonged exposure to early life adversity results in structural and functional alterations in stress-sensitive regions of the brain such as the hippocampus, the amygdala, and the prefrontal cortex [32,52,53]. These regions are thought to play important roles in the regulation of the SAM and HPA axes.

- In the prefrontal cortex, chronic exposure to adversities has been shown to cause reduced prefrontal cortex synaptic plasticity in children and has been associated with selective prefrontal cortex atrophy in adults.
- In the amygdala, chronic exposure to stress has been linked to increased amygdala volume in children and atrophy in adults.
- In the hippocampus, prolonged stress exposure has been associated with reduced hippocampal volume in adults.

Endocrine system

In the endocrine system, prolonged or severe exposure to early life adversity is associated with changes in hormonal levels consistent with chronic activation of the HPA axis: increased CRH levels, lower morning cortisol levels, and elevated afternoon cortisol levels. These changes result in flatter circadian variation and greater daily secretion of cortisol [54], and overall disruption of the feedback inhibition of cortisol on the HPA axis [55,56]. Over time, HPA axis hyperactivity may recede, and in severe cases of prolonged and/or intense toxic stress response, the activity of the HPA axis decreases, to very low or deficient hormonal levels [54].

Immune system

The chronic dysregulation of the HPA axis has profound effects on the immune and inflammatory response, because virtually all the components of the immune response are influenced by glucocorticoids. The neuroendocrine immune circuitry interacts through cytokines, chemical signals that play a key role in regulating both innate and acquired immunity [57] and are essential to development and metabolism of most body tissues and organ systems [58]. The activation of the sympathetic nervous system during a stress response triggers a sustained elevation in the inflammatory response in the organism by inducing the secretion of proinflammatory cytokines in the systemic circulation [59,60]. Proinflammatory cytokines are produced by the immune system to prevent possible infections and are responsible for the activation of complex adaptive response known as sickness behavior, which enhances recovery by conserving energy to combat acute inflammation through the activation of the thermoregulatory and appetite-satiety centers in the brain [61]. Proinflammatory cytokines also interact with the HPA axis during an immune response [62]. They activate the HPA axis to secrete cortisol and, cortisol participates in the negative feedback inhibition to shut down the HPA axis and the inflammatory response, after the threat is removed [62,63].

The prolonged dysregulation observed during a chronic toxic stress response inhibits anti-inflammatory pathways and results in elevation of inflammation

levels, such as elevated levels of C-reactive protein (CRP) and proinflammatory cytokines [56,64–66]. In addition, prolonged exposure to stress has been associated with impaired cell-mediated acquired immunity due to the combined effects of glucocorticoid and catecholamine suppression of innate and cellular immunity (T cells) and stimulation of humoral immunity (B cells) [67,68].

TOXIC STRESS AND CLINICAL IMPLICATIONS

Alterations to the nervous, endocrine, and immune systems that stem from a toxic stress response influence multiple organ systems. In adults, these multisystemic changes have been linked to an increased risk of developing chronic disorders, such as metabolic syndrome, cardiovascular disease, allergic and atopic disease, inflammatory diseases, autoimmune diseases, as well as cognitive, mental, and behavioral disorders.

Multisystemic alterations

The prolonged activation of a toxic stress response is associated with systemic alterations because it results in the excessive or deficient secretion of stress-induced hormones (eg, cortisol), catecholamines (eg, norepinephrine and epinephrine), and inflammatory factors (eg, proinflammatory cytokines, CRP) [69]. These alterations impact biological and behavioral functions across systems, including those primarily regulated by the nervous, endocrine, and immune systems.

Neurologic, psychiatric, and behavioral alterations

Promising research suggests that cytokines and altered levels of stress-induced hormones participate in the pathophysiology of developmental, cognitive, mental, and behavioral disorders in children and adults [70–74]. A dysregulation of the HPA axis is associated with behavioral and cognitive changes in the prefrontal cortex, amygdala, and hippocampus. In the prefrontal cortex, chronic exposure to adversities has been shown to cause impairment of executive functions, such as attention, reasoning, self-regulation (eg, impulse control), working memory, and problem solving. In the amygdala, chronic stress response causes alterations in behavioral responses, such as enhanced awareness and responsiveness to potential threats (hypervigilance), an enhanced response to stimuli that elicit a fear response but have not been previously witnessed (unlearned fear), and learned behavioral responses to predicted threats (fear conditioning). In the hippocampus, prolonged stress response can cause behavioral changes such as impaired memory and learning [53].

Early life adversity has also been associated with an increased incidence of adult psychopathology that is linked to a dysregulated HPA axis function. Adolescents exposed to severe adversity have a greater incidence of suicidal ideation, suicide attempts, and dysthymia. A spectrum of other conditions may also be associated with increased and prolonged activation of the HPA axis, including anorexia nervosa, obsessive-compulsive disorder, panic anxiety, excessive exercise, and chronic active alcoholism [40]. In addition, poor caregiving quality can have early effects on HPA axis regulation and is suggested as one of the mechanisms contributing to heightened risk of mental health

disorders, such as posttraumatic stress disorder, chronic anxiety, melancholic depression, eating disorders, substance and alcohol abuse, and personality and conduct disorders [75,76].

Similarly, early adversity is frequently associated with disruption of early caregiving interactions, which may alter the development and expression of certain social behaviors. Emerging evidence suggests that failures in regulation of the HPA axis in young children may play a role in shaping the mesocorticolimbic circuits (VTA dopaminergic system) involved in processing threatening experiences encountered later in life, which results in a corresponding labile mesocorticolimbic dopaminergic system and possible dysphoria. These effects, among others, may be mediated via changes in the release of stress-induced hormones such as vasopressin and serotonin. Early social experience can alter concentrations of vasopressin, and serotonin, an essential neurotransmitter for the regulation of emotional and social behaviors, in particular, aggression. Alterations of the release of serotonin have been reported in humans exposed to early adversities such as maltreatment [77]. For example, patients with borderline personality disorder who experienced childhood maltreatment were found to have altered serotonin activity and increased aggressive and impulsive behaviors [78].

Finally, HPA axis dysregulation may also be associated with a peripheral neuroendocrine effect on the gastrointestinal system. In particular, HPA axis activation induces inhibition of gastric acid secretion and emptying while stimulating colonic motor function. The excessive secretion of CRH due to a hyperactive HPA axis may also play a role in the stress-induced colonic hypermotility of patients with irritable bowel syndrome [40].

Endocrine, metabolic, and reproductive alterations

Research continues to link the effects of HPA axis disruption on the immune response with the pathogenesis of metabolic disease and an increase of cardiovascular disease risk [79,80]. In particular, the dysregulation of the HPA axis and the resulting chronically elevated levels of cortisol have been associated with increased tissue sensitivity to glucocorticoids and chronic activation of the glucocorticoid receptors. This chronic and persistent activation is found to be indirectly involved in the pathogenesis of individual components of the metabolic syndrome: obesity, insulin resistance, glucose intolerance, dyslipidemia, and hypertension. Furthermore, glucocorticoids and epinephrine have direct effects on the heart and blood vessels, and high levels of these factors have been found to influence vascular function, early atherogenesis, and vascular remodeling [81–83], increasing the risk for cardiovascular and cerebrovascular diseases.

Thyroid function is also inhibited during stress. Activation of the HPA axis is associated with decreased production of thyroid-stimulating hormone as well as inhibition of peripheral conversion of the relatively inactive thyroxine to the biologically active triiodothyronine. These alterations may be due to the increased concentrations of CRH-induced glucocorticoids and may result in subclinical or clinical hypothyroidism [40,84].

The reproductive system is inhibited at all levels by various components of the HPA axis. HPA axis activation suppresses the secretion of gonadotropin-releasing hormone either directly or indirectly. Glucocorticoids also exert an inhibitory effect on the gonads. During inflammatory stress, for example, the elevated concentrations of cytokines also result in suppression of reproductive function [40,84], which may explain the relationship between high levels of stress and irregularities of the menstrual cycle frequently observed clinically in adolescents.

Immune and inflammatory alterations

A healthy development of the child's immune system depends on a series of essential changes, such as the adaptive immune system response that regulates the immune response toward humoral (B cells and antibodies) or cellular immunity (T cells and T-helper 1 and T-helper 2 response) [85]. Dysregulation of this adaptive response toward an excessive T-helper 2 cell response early in life creates life-long immune hyperreactivity, which increases the risk of developing allergies and asthma [85,86]. Children exposed to early adversity are more likely to develop or report asthma and have poor control of asthma symptoms. In addition, children exposed to early adversity are more likely to have elevated inflammatory markers (eg, cytokines, CRP) and greater inflammatory response to stress as adults, increasing the risk of developing inflammatory and autoimmune diseases [87–90].

Over time, a prolonged stress response has also been associated with impaired cell-mediated acquired immunity due to the combined effects of glucocorticoids and catecholamines, which cause suppression of innate and cellular immunity [67,68]. The effects of stress-related immunosuppression facilitate diseases related to deficiency of the humoral and cellular immune responses, such as common cold, tuberculosis, and certain tumors [91]. In addition to the direct effects of toxic stress, children at highest risk of early adversity are also more likely to be exposed to environmental toxins, such as secondhand smoke and environmental pollution, which increase the risk of developing a hyperreactive immune response [92,93]. Sensitization to these allergens early in life has been correlated with the development of allergic and atopic disease [92].

Fig. 4 summarizes the complex interplay of the mechanisms observed during a chronic toxic stress response and the associated clinical implications.

Genetic factors and epigenetic modifications

The stress response of an individual is determined by multiple factors, many of which are inherited. Genetic polymorphisms, such as those of stress-induced hormones, and their receptors and/or regulators, account for much of the observed variability in the function of the stress response. These polymorphisms are an expression of a complex continuum that ranges from extreme resilience to extreme vulnerability to stress and adversity. Gene-environment interactions likely reflect genetic moderation of the brain and body functional response to stress, including early life stress. It is conceivable that these

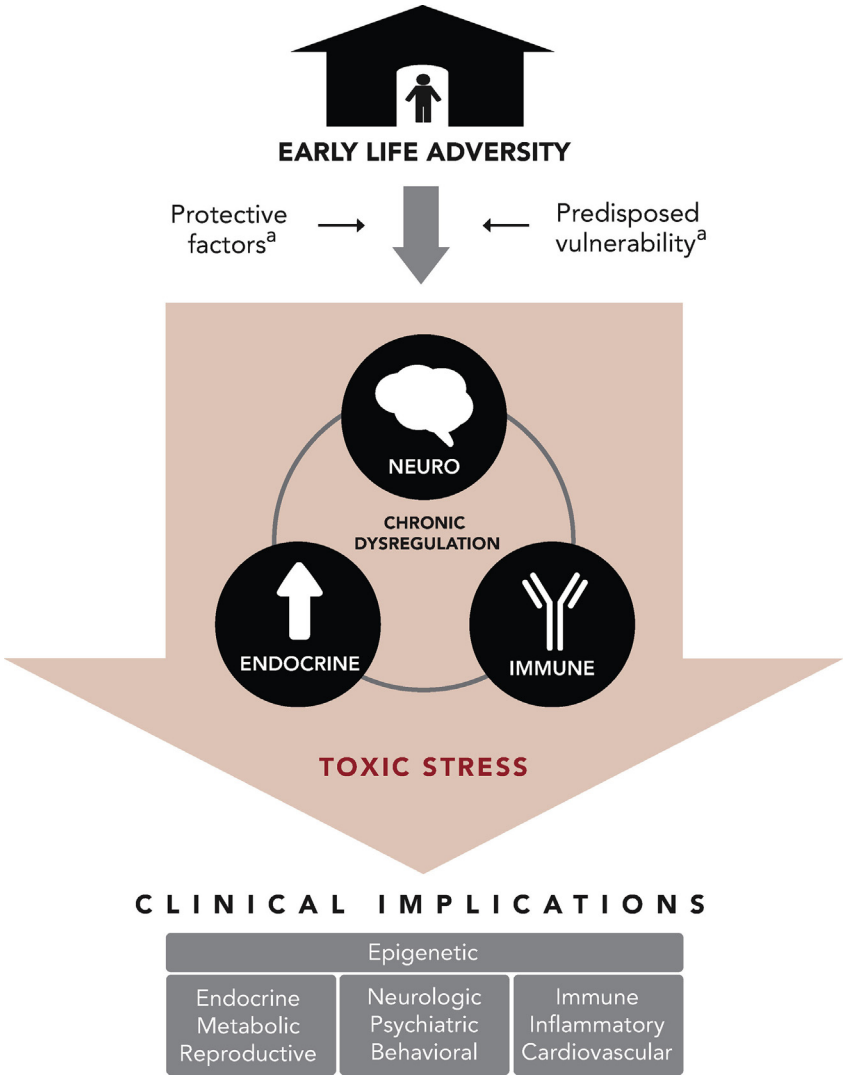


Fig. 4. Overview of toxic stress. [a]Social, biological, genetic factors.

genotype-related alterations underlie individual differences in the susceptibility to develop a toxic stress response.

Additionally, epigenetic regulation in childhood play a role in damaging the systems involved in the organism's future response to stress in adulthood. Epigenetics is defined as heritable changes in gene activity and expression that occur without alteration in DNA sequence. These changes are tightly regulated by 2 major epigenetic modifications: DNA methylation and histone modifications. Epigenetic regulation typically occur in the cells

of multiple organ systems, therefore influencing how these structures develop and function. Data suggest that these chemical modifications are highly responsive to early adversity. Some genes can only be modified epigenetically during sensitive periods of development [94–99]. Epigenetic changes that occur early in life, when these organ systems are still developing, can have important effects on long-term physical and mental health outcomes [100]. Therefore, epigenetic regulation caused by a chronically activated toxic stress response during sensitive periods of development affect how the systems respond to stress in adulthood and can result in increased risk of chronic disease.

The brain is particularly sensitive to early life adversity during sensitive periods of development, which influences how its architecture matures and functions. Exposure to severe and prolonged adversity in childhood can lead to long-lasting changes in the brain that may impact how the nervous system responds to future adversity [28]. For example, in animal models and studies with children in foster care, variations in maternal care soon after birth have demonstrated the potent role of epigenetic programming in an offspring's behavioral and neuroendocrine stress responses [29,76,101]. In animals, stressful experiences soon after birth have been shown to cause epigenetic modifications that alter the chemical structure of receptors in the brain, which regulates the activation of the fight-or-flight response. These modifications have been shown to result in prolonged stress responses [101–103].

In addition, in animals, exposure to strong stressors has been correlated with epigenetic changes in brain architecture, brain chemistry, and behaviors that resemble anxiety and depression in humans [104–109]. Human studies have shown associations between severe adverse experiences in children and increased risk for later mental illnesses, including generalized anxiety disorder and major depressive disorder [110–112]. Chronically dysregulated stress responses can also result in epigenetic alterations that have been associated with increased risk of other chronic diseases, such as asthma, hypertension, heart disease, and diabetes [28,110–118].

Conversely, a supportive environment can generate positive epigenetic changes [119]. Recent research demonstrates that even after epigenetic modifications, it may still be possible to reverse negative changes and restore normal physiologic function through positive interactions between child and caregiver [104,120]. In animals, examples of these positive epigenetic modifications are the development of cognitive skills, like learning and memory [121]. Interactions between early adversity, genotype, and epigenetic changes are an important and promising area of future research in humans, due to their it has direct implications for developing new interventions to prevent physical and mental illnesses that are due in part to epigenetic modification.

DISCUSSION

ACEs, including abuse, neglect, household dysfunction, and other early life adversities, have been associated with long-term negative health outcomes. A

toxic stress response has been implicated as a contributing factor to the development of these outcomes. The physiologic response to a stressor is determined by multiple factors, including the duration and severity of the exposure; social, biological, and genetic protective factors and vulnerabilities; and developmental factors. A prolonged stress response can result in the chronic activation of the neuroendocrine immune systems involved in the stress response. If exposure to a stressor is time limited or if the individual has appropriate coping mechanisms, allostatic processes can facilitate an adaptive stress response and return the organism to homeostasis. Prolonged or severe exposure to a stressor, however, can cause a dysregulation in the neuroendocrine immune circuitry, damaging the inhibition feedback and regulation mechanisms and creating a maladaptive, or toxic, stress response. This toxic stress response may produce an excess or deficiency in stress-induced hormones and neurotransmitters, which, when experienced during sensitive periods of development in childhood, can become incorporated into the developing biological systems. This altered availability of hormones and neurotransmitters induces lasting changes that affect multiple organ systems and functions, including brain architecture, endocrine system regulation, and immune response. The alterations of multiple organ systems, in conjunction with genetic vulnerability and epigenetic regulation, place an individual at risk for negative physical, mental, and behavioral health outcomes well into adulthood.

Despite increased awareness of toxic stress, many limitations restrict current understanding of the topic and clinical implications for pediatric health. Because the factors influencing the development of toxic stress and disease are multifactorial, the field has been challenged in defining the precise connections between genetic vulnerability to stress, alterations in the molecular and neuroendocrine immune pathways that modulate the stress response, and the clinical presentation of these alterations. Further clarification of the role that toxic stress plays, either as an effect modifier or as part of the causal pathway for disease, will help practitioners better identify appropriate screening and treatment modalities and ultimately lead to more effective policies that address the effects of ACEs. Another limitation is the lack of information on effective interventions. Evidence from animal models shows that bolstering the child-caregiver relationship can reverse the effects of adversity at both physiologic and epigenetic levels and improve health outcomes [122,123]. Further research on the neurobiology of resilience and protective mechanisms for development is needed to better understand how interventions can both prevent and heal the effects of a toxic stress response.

As researchers work to address the gaps in understanding, policymakers and practitioners are seeking ways to address the effects of adversity and toxic stress in diverse settings. The American Academy of Pediatrics has called on pediatricians to screen for precipitants of toxic stress [124]. Assessing a patient's history of early adversity places the mental and social aspects of an individual's life firmly into the physical health sphere, enabling medical providers to use the

biopsychosocial model of health care more effectively. Through this model, providers can raise awareness among patients of the effects of early adversity and stress on children's physical health. Medical providers can also use this patient history to consider modifications to standard prevention or screening advice for various medical conditions. In addition, using the biopsychosocial model of toxic stress to address clinical conditions that are traditionally understood as behavior dependent (eg, obesity) can help shift the stigma of adversity and improve engagement in treatment options for both children and their caregivers.

A critical next step for the field is the development of clinical diagnostic criteria for toxic stress. As the research on toxic stress moves forward, standardized ways of identifying patients at risk using well-defined risk factors and/or biomarkers will help better elucidate the public health challenge that practitioners and policymakers face. Clinical diagnostic criteria will enable researchers, medical practitioners, and policymakers to work together to inform prevention and treatment of health outcomes associated with early life adversity. Standardized criteria will also allow for the development of interventions focused on helping children reduce acute physiologic responses to stressors, develop natural protective mechanisms of resilience and prevent long-term pathogenic processes from initiating or worsening.

Although the intricacies of the physiologic impact of adversity and toxic stress are still being investigated, the science is clear: early adversity dramatically affects health across a lifetime. It is critical for practitioners and policymakers to move forward to prevent, screen, and heal the effects of early adversity and toxic stress.

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