The Biology of Toxic Stress

Scientific progress over the past several decades has allowed researchers to characterize, with greater precision than ever before, the extent to which our experiences and environments shape our biology. Advances in functional neuroimaging, developmental neurobiology, genomics, epigenomics, transcriptomics, proteomics, and metabolomics have begun to decode the complex mechanisms by which early adversity can become biologically embedded and influence life-course health and even the health of the next generation.

The growing body of evidence linking environmental factors, including social and economic conditions, to immediate and long-term health outcomes allows healthcare providers and public health systems to better serve patients and communities. Demystifying the root causes of illness and behavior can lead to more targeted clinical and policy interventions as well as greater compassion, patience, and the opportunity for relational healing through caring relationships. Across the healthcare landscape, modern precision medicine approaches and technologies are facilitating targeted prevention, pinpoint diagnostics, and individually tailored therapies.[65] At the cutting edge, the research community continues to deliver strong evidence that individuals with Adverse Childhood Experiences (ACEs) and likely toxic stress are at much higher risk for health and social challenges for decades to come, and that increased risk may be passed down to subsequent generations. What follows is an overview of scientific studies describing the biological mechanisms by which early adversity, through the toxic stress response, affects health.

Stress is defined as a "real or interpreted threat to the physiological or psychological integrity of an individual which results in physiological and/or behavioral responses."[66] Stressors include experiences as diverse as navigating a new environment, running a marathon, witnessing violence, or enduring a physical injury. The body reacts to stress via a complex process of physiological and behavioral adaptation known as **homeostasis**, which allows biology to remain within physiologic parameters necessary for life.[67] An example of homeostasis is the activation of perspiration and thirst as body temperatures rises on a hot day. These responses serve to cool the body and maintain temperatures within a preset normal range.

More recently, the term **allostasis**[66] was developed by McEwen and colleagues in recognition that certain circumstances result in physiological adaptations that result in new biological set points that may be temporary or permanent. An example of allostasis is the many hormonal and physiologic changes associated with lactation when an infant is born. In response to the birth of the child, the mother's body establishes and maintains new biological set points necessary to support milk production and infant feeding. The energy required to achieve allostasis is known as **allostatic load**.[67]

In response to a stressor, the body releases stress hormones, including adrenaline (also known as epinephrine) and cortisol, that activate a range of biological responses: heart rate and blood pressure increase, brain structures associated with threat and vigilance become more active, aspects of learning and memory are altered, and the parts of the brain that facilitate impulse control, judgment, and executive function become less active.[68-72] Blood is more efficiently channeled to the parts of the brain, organs, and muscles involved in the fight-or-flight response.[73] Elsewhere in the body, respiration and immune activity increase, digestion slows, and the reproductive system nearly shuts down completely.[74] These responses are essentially identical in mammals, birds, fish, and reptiles, and are central to surviving the types of stressors typically experienced by organisms, namely short-term, physical emergencies. Humans, in contrast, activate the same physiological responses during acute or chronic, non-physical, psychosocial stress.

As the crucial concept in the field, when the stress response is activated too frequently, intensely, or chronically, allostasis may occur, resulting in new biological set points being "wired" as an adaptation to respond to stressful environments. The stress response, which is life-saving when activated in the short term, as in most organisms, becomes health-damaging when activated chronically, producing a state of pathologically heavy allostatic load.[75-77] For example, in the short term, stress hormones increase blood pressure, which can bring greater blood flow to muscles to save an animal sprinting for its life, but when activated chronically, can lead to increased wear and tear on blood vessels and damage to the cardiovascular system.

WHAT IS "TOXIC STRESS"?

The biological stress response has been characterized as falling into three types: positive, tolerable, and toxic (see **Figure 4**).[78] Not all stress is bad. Some stress is a necessary and even essential part of growth and development; it can help us transiently mobilize energy and increase focus to perform better at the task at hand, such as an upcoming test, the big game, or a presentation at work. The **positive stress response** is characterized by brief elevations in stress hormones,

heart rate, and blood pressure in response to a routine stressor. The **tolerable stress response** "activates the body's alert systems to a greater degree as a result of more severe, longer-lasting difficulties, such as the loss of a loved one, a natural disaster, or a frightening injury. If the activation is time-limited and buffered by relationships with adults who help the child adapt, the brain and other organs recover from what might otherwise be damaging effects."[79]

The **toxic stress response** is defined by the National Academies of Science, Engineering, and Medicine's (NASEM) 2019 consensus report as "prolonged activation of the stress response systems that can disrupt the development of brain architecture and other organ systems, and increase the risk for stress-related disease and cognitive impairment, well into the adult years… For children, the result is the disruption of the development of brain architecture and other organ systems and an increase in lifelong risk for physical and mental health disorders."[23]

Adversity experienced during the prenatal or early life periods, without adequate buffering protections of safe, stable, and nurturing relationships and environments, can alter the biological stress response, disrupt the development of neuro-endocrine-immune-metabolic and genetic regulatory mechanisms, and lead to toxic stress, thus increasing risk for poor health.

The term toxic stress is often mistakenly used to refer to the drivers of stress or the stressors. In fact, toxic stress refers to the dysregulated biological stress response and the concomitant long-term changes in physiology (**Figure 5a,b**).[6-12,23] Frequent, chronic, or intense stress in a child's environment may tip the balance

TOXIC STRESS RESPONSE

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CRITICAL PERIOD

A time in development when the presence or absence of an experience results in irreversible change.[83,84]

SENSITIVE PERIOD

A time when the brain is particularly responsive to a stimulus in the environment.[84]

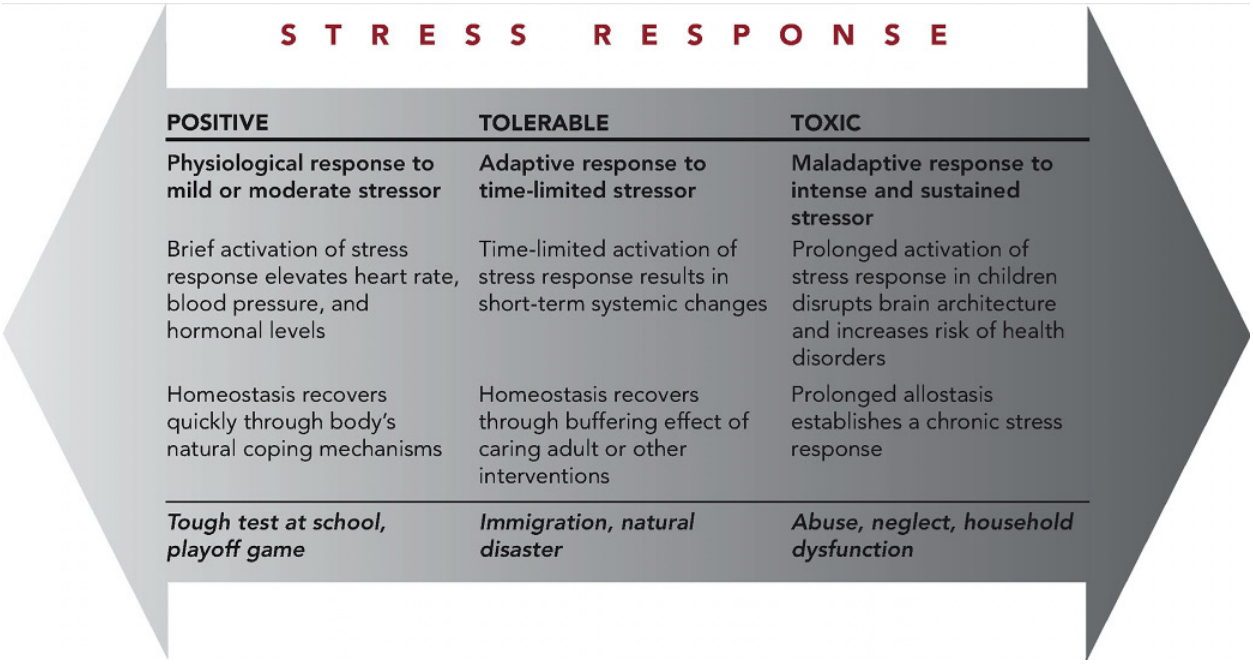
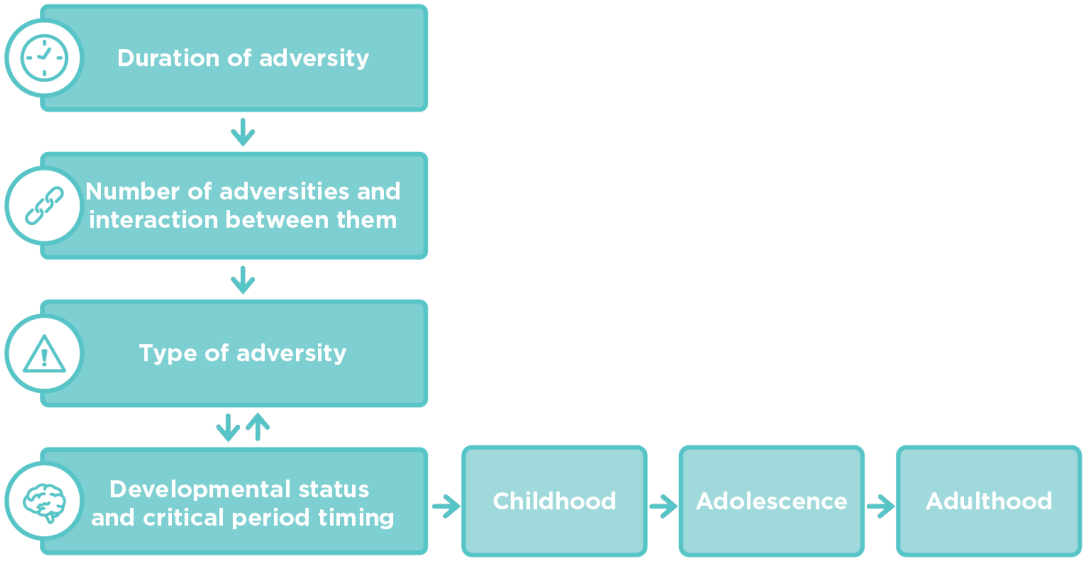


Figure 4. *Stressors such as homework and training in team sports are normative, even positive experiences, and help build adaptive capacities that result in resilience. Tolerable stressors may occur due to early experiences such as moving, routine family hardship, and in some cases, natural disasters. These are time-limited and, with enough positive support, are able to be overcome. Toxic stress may arise due to ACEs or significant stressors such as exposure to discrimination or poverty that are not sufficiently buffered by a positive supportive environment and other interventions. Figure reproduced with permission from Elsevier.*[6]

from the positive or tolerable stress response to a toxic stress response, leading to stress-related disease and cognitive impairment.[3,6] While the term "toxic stress" was originally coined by the National Scientific Council on the Developing Child[33] as a means to describe the developmental changes associated with prolonged adversity in a policy context, it is now recognized that the accumulated changes to the physiologic stress response system, as well as brain and other organ system development, represent a health condition with clinical implications.[6-12,80]

Children are especially susceptible to effects of adversity because their brains and bodies are developing, that is, laying a foundational architecture for a lifetime of health and experiences. Critical and sensitive periods of development mark distinct and time-limited periods when children's growth and maturation is, respectively, dependent on or heavily influenced by interactions with the environment and people around them.[81,82] A **critical period** is a time in development when the presence or absence of an experience results in irreversible change.[83,84,1608,1609] Binocular vision (the ability of the brain to consolidate input from the two eyes into a single,



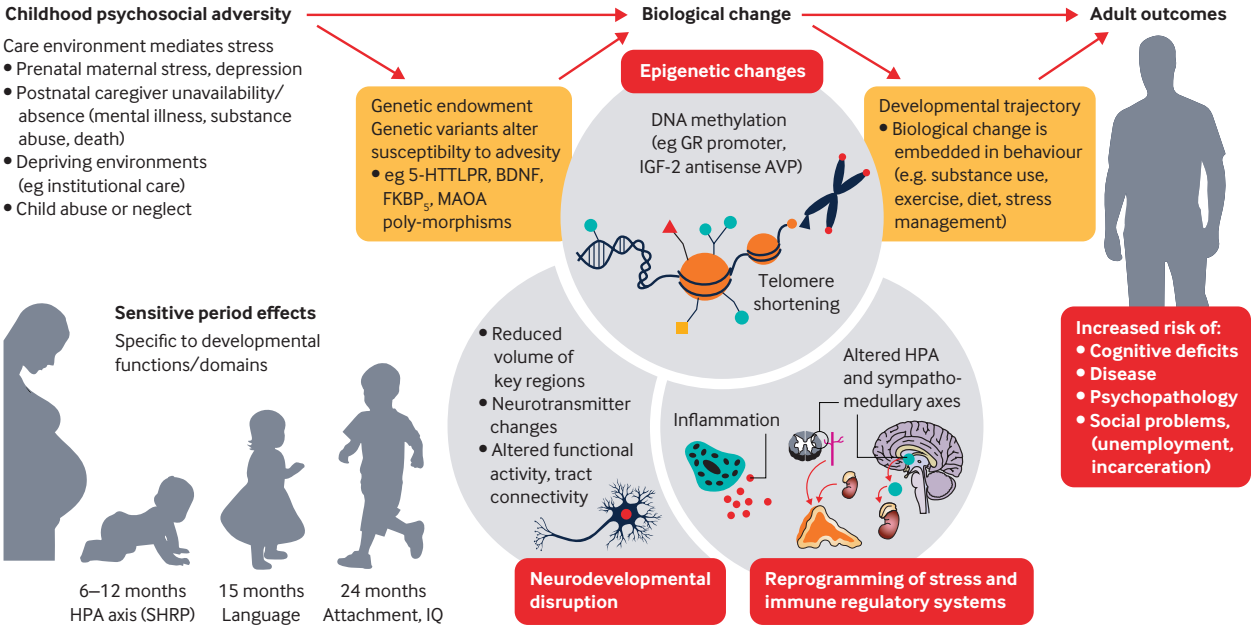


Figure 5a,b. *A depiction of how childhood adversity (important variables include: duration, number, interactions, and types) interacts with an individual's genetic endowment and developmental trajectory to lead to a variety of biological changes called the toxic stress response, including neuro-endocrine-immune-metabolic and genetic regulatory disruptions, to increase risk for lifelong health and social problems. Reproduced under a creative commons open access license from The BMJ.*[103]

integrated, three-dimensional picture) is an example of a developmental process that has a critical period. If a child has misalignment of one or both eyes that is not corrected within a specific window of time (typically by age eight), then the ability of the brain to form a 3-D image from ocular inputs is lost, even if the eye alignment is subsequently corrected. Similarly, a **sensitive period** is a time when the brain is particularly responsive to a stimulus in the environment.[23,84] Unlike critical periods, the window doesn't entirely close at the end of the sensitive period, but the brain's responsiveness diminishes significantly. Language acquisition is an example of a developmental process that has a sensitive period. Learning a new language happens more quickly and with less effort in early childhood due to high levels of neuroplasticity in the brain centers governing language, but the ability to acquire new languages does continue throughout life, albeit at a reduced level. Experiencing adversity during critical and sensitive periods is therefore more likely to lead to long-term changes in epigenetics, neurophysiology, endocrine systems, immune function, metabolism, and other biological systems.

The more ACE categories to which a person is exposed, the more likely it is that they will develop a toxic stress response and that health conditions also known as ACE-Associated Health Conditions (AAHCs) will develop earlier on and more severely than if the individual had not been exposed. These conditions include cardiovascular disease, chronic obstructive pulmonary disease (COPD), liver disease, cancer, diabetes, obesity, cognitive impairments, risky sexual behaviors, early and high-risk substance use, depression, suicidality, poor self-rated health, and premature mortality.[2-5,13,16,29,30,63,64,85] The list of currently understood AAHCs for adult and pediatric patients in presented in **Tables 2** and **3**.

Cumulative adversity is also associated with poorer educational and social outcomes, including learning, developmental, and behavior problems, high school noncompletion, unemployment, low life satisfaction, poverty, and felony charges—many of which can serve as additional vectors for the intergenerational transmission of adversity.[2,16,17,34-40]

It is important to note that ACE exposure alone does not determine or foretell an individual's future health or life outcomes. Rather, the risks associated with ACE exposure are modulated by multiple factors, such as biological susceptibility, which includes genetic material inherited from one's parents, and protective factors, such as supportive relationships, environments, and community resources.[36,41-46,87] One example of biological susceptibility is the presence of several versions of the serotonin transporter gene, which control the concentration of the neurochemical serotonin, which is important for mood, reward, and learning. Those with one form of the gene are more likely to develop psychopathology, such as depression, after stressful situations than those with a different version of the gene.[88-95]

ACE-Associated Health Conditions: Pediatrics

Symptom or Health Condition	For ≥ X ACEs (compared to 0)	Odds Ratio
Asthma[26, 33]	4	1.7 - 2.8
Allergies[33]	4	2.5
Dermatitis and eczema[39]	3*	2.0
Urticaria[39]	3*	2.2
Increased incidence of chronic disease, impaired management[25]	3	2.3
Any unexplained somatic symptoms[25] (eg, nausea/vomiting, dizziness, constipation, headaches)	3	9.3
Headaches[33]	4	3.0
Enuresis; encopresis[5]	–	–
Overweight and obesity[3]	4	2.0
Failure to thrive; poor growth; psychosocial dwarfism[5, 2, 41]	–	–
Poor dental health[16, 22]	4	2.8
Increased infections[39] (viral, URIs, LRTIs and pneumonia, AOM, UTIs, conjunctivitis, intestinal)	3*	1.4 - 2.4
Later menarche[40] (≥ 14 years)	2*	2.3
Sleep disturbances[5, 31]	5**	PR 3.1
Developmental delay[30]	3	1.9
Learning and/or behavior problems[3]	4	32.6
Repeating a grade[15]	4	2.8
Not completing homework[15]	4	4.0
High school absenteeism[33]	4	7.2
Graduating from high school[29]	4	0.4
Aggression; physical fighting[28]	For each additional ACE	1.9
Depression[29]	4	3.9
ADHD[42]	4	5.0
Any of: ADHD, depression, anxiety, conduct/behavior disorder[30]	3	4.5
Suicidal ideation[28]	For each additional ACE	1.9
Suicide attempts[28]		1.9 - 2.1
Self-harm[28]		1.8
First use of alcohol at < 14 years[7]	4	6.2
First use of illicit drugs at < 14 years[10]	5	9.1
Early sexual debut[21] (<15-17 y)	4	3.7
Teenage pregnancy[21]	4	4.2

Table 2. *ACEs are associated in a dose-response fashion with many leading causes of poor health in children; the odds ratios represent data on health risks in those with four or more ACEs, relative to those with none. Reproduced with permission from ACEs Aware.*[86]

Accumulating positive experiences during childhood can buffer the developing brain and body from the harmful effects of stress—in other words, they build resilience.[42,96,97] **Resilience** is the ability to withstand or recover from stressors, and results from a combination of intrinsic factors, extrinsic factors (like safe, stable, and nurturing relationships with family members and others), and predisposing biological susceptibility.[42,98,99] Of note, while the term resilience is often considered in the mental health and behavioral domains, scientific advances in understanding of the impact of stress on neuro-endocrine-immune-metabolic and genetic regulatory

ACE-Associated Health Conditions: Adults

Symptom or Health Condition	Odds Ratio (excluding outliers)
Cardiovascular disease[21] (CAD, MI, ischemic heart disease)	2.1
Tachycardia[37]	≥ 1 ACE: 1.4
Stroke[20]	2.0
Chronic obstructive pulmonary disease (emphysema, bronchitis)[21]	3.1
Asthma[43]	2.2
Diabetes[21]	1.4
Obesity[20]	2.1
Hepatitis or jaundice[1]	2.4
Cancer, any[21]	2.3
Arthritis[32, 7] (self-reported)	3 ACEs, HR: 1.5 ≥ 1 ACE: 1.3
Memory impairment[20] (all causes, including dementias)	4.9
Kidney disease[43]	1.7
Headaches[11]	≥ 5 ACEs: 2.1
Chronic pain, any[38] (using trauma z-score)	1.2
Chronic back pain[38] (using trauma z-score)	1.3
Fibromyalgia[37]	≥ 1 ACE: 1.8
Unexplained somatic symptoms, including somatic pain, headaches[20, 2]	2.0 - 2.7
Skeletal fracture[1]	1.6 - 2.6[20]
Physical disability requiring assistive equipment[23]	1.8
Depression[21]	4.7
Suicide attempts[21]	37.5
Suicidal ideation[20]	10.5
Sleep disturbance[20]	1.6
Anxiety[21]	3.7
Panic and anxiety[20]	
Post-traumatic stress disorder[37]	4.5
Illicit drug use[21] (any)	5.2
Injected drug, crack cocaine, or heroin use[21]	10.2
Alcohol use[21]	6.9
Cigarettes or e-cigarettes use[35]	6.1
Cannabis use[35]	11.0
Teen pregnancy[21]	4.2
Sexually transmitted infections, lifetime[21]	5.9
Violence victimization[21] (intimate partner violence, sexual assault)	7.5
Violence perpetration[21]	8.1

Table 3. *ACEs are associated in a dose-response fashion with many leading causes of poor health in adults; the odds ratios represent data on health risks in those with four or more ACEs, relative to those with none. Reproduced with permission from ACEs Aware.*[86]

health compel advancement of the definition of resilience to also include these domains as well.

A nurturing parent or caregiver is a critically important resilience factor for children, turning potentially toxic stress into tolerable stress.[41,43,44,46,100] Other factors that reduce the likelihood of developing a toxic stress response include freedom from discrimination, supportive friend networks, safe neighborhoods, and community resources, like access to high-quality healthcare, nutrition, and

child care.[45,101] At the molecular level, resilience arises from a combination of neural, hormonal, immune, metabolic, epigenetic, and genetic factors that interact with environmental influences and foster an individual's ability to adapt in a healthy manner. In order to determine why some individuals are less sensitive to stress than others, researchers have sought methods to peer more deeply into biological mechanisms and observe the inner workings of the cell and other biological systems to, in the metaphor often used, "get underneath the skin" in understanding how ACEs lead to AAHCs.[102] These mechanisms by which toxic stress is embedded in the functioning of different organ systems, and how those processes affect health and behavior, are discussed below (**Figure 5**, **Table 4**).

TOXIC STRESS: NEUROLOGIC, NEUROENDOCRINE, AND NEUROPSYCHIATRIC EFFECTS

HPA and SAM axes

We react to perceived threats with the fight-flight-or-freeze response—preparing our bodies to be able to take action to oppose danger by running away, or remaining in place to challenge the threat. Most of the biological reactions that facilitate these normal responses are driven by two main systems: the sympatho-adreno-medullary (SAM) axis, which makes the stress hormone adrenaline and hypothalamic-pituitary-adrenal (HPA) axis, which makes the stress hormone cortisol. These circuits originate in the brain and are essential for adaptive biological responses. Both the HPA and SAM systems are normally active at baseline levels, but in response to stress, activity intensifies. When activated too frequently or for too long, these systems can become dysregulated.

When the SAM axis is activated, the sympathetic nervous system (SNS), which connects to nearly all the organs in our body, directly releases the neurochemical noradrenaline (also known as norepinephrine), causing the adrenal glands to release adrenaline (also known as epinephrine). These chemicals typically act within seconds to minutes. The release of adrenaline rapidly and systemically prepares multiple organ systems to fight or to flee a threat by enhancing alertness, increasing heart rate, blood pressure, and respiration, funneling oxygenated blood and cellular fuel to the brain and skeletal muscles in the arms and legs, increasing immune activation, and temporarily pausing non-essential functions, including suppressing appetite and reproductive drive.[74,104-106] Briefly, the HPA axis is activated when multiple brain regions identify a threat. The hypothalamus responds by releasing corticotropin-releasing hormone (CRH), which triggers the pituitary gland to release adrenocorticotropic hormone (ACTH), which, in turn, stimulates the adrenal glands to release cortisol, which works over hours to days. During stressful episodes, cortisol triggers the liver, fat cells, muscles, and

System	Mechanism(s)	Health Impact
Neurologic; neuroendocrine	Dysregulation of the sympatho-adren-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) axes, with long-term changes in regulation of key hormones, including cortisol and adrenaline; autonomic imbalance	Difficulty modulating, sustaining, or dampening the stress response; heightened or blunted stress sensitivity
	Altered reactivity and size of the amygdala	Increased fear responsiveness, impulsivity, and aggression
	Inhibition of the prefrontal cortex	Impaired executive function, with poorer planning, decision-making, impulse control, and emotion regulation
	Hippocampal neurotoxicity	Difficulty with learning and memory
	Ventral tegmental area (VTA) and reward processing dysregulation	Increased risky behaviors and risk of addiction
Immunologic; inflammatory	Increased inflammatory mediators and markers, especially of the Th2 response; inhibition of anti-inflammatory pathways; gut microbiome dysbiosis	Increased risk of infection, auto-immune disorders, cancers, chronic inflammation; cardiometabolic disorders
	Changes in growth hormone, thyroid hormone, and pubertal hormonal axes	Changes in growth, development, basal metabolism, and pubertal events
Endocrine; metabolic	Changes to leptin, ghrelin, lipid and glucose metabolism, and other metabolic pathways	Increased risk of overweight, obesity, cardiometabolic disorders, and insulin resistance
	Sustained changes to the way DNA is read and transcribed	Mediates all aspects of the toxic stress response
Epigenetic; genetic	Sustained changes to the way DNA is read and transcribed	Mediates all aspects of the toxic stress response
	Telomere erosion, altered cell replication, and premature cell death	Increased risk for disease, cancer, and early mortality

Table 4. *Biological systems disrupted by toxic stress.*

the pancreas to increase blood sugar levels available to the brain and skeletal muscles, which boosts energy levels and readies the body to respond to a threat. Cortisol also increases blood pressure and cardiac output, while suppressing sleep, immune, reproductive, and growth functions.[74] The fact that most human cells are sensitive to cortisol helps explain the wide-ranging impacts of the hormone on the body during normal times, including on metabolism, immune and inflammatory mechanisms, reproductive function, cognition, mood, sleep and wakefulness, and motivation.

When fight or flight is not possible, the freeze response may be employed. The freeze response can consist of either "playing dead," which involves dissociating and/or fainting, conserving energy and releasing endogenous opioids, or a "frozen stiff" state, which involves heightened awareness with an inability to move.[107,108]

Normal regulation of the stress response works much like a thermostat, in which increasing levels of adrenaline and cortisol trigger the brain to turn off the stress response in a process called feedback inhibition, just as a thermostat turns off the heat when the desired temperature is reached. Thus, homeostasis is restored.

However, chronic stress not only activates the stress response repeatedly, but gradually impairs feedback inhibition, compromising an organism's capacity to recover back to baseline after a stressor.[75-77] For example, exposure to ACEs and other adversities may be associated with reduced responsiveness of the brain to the hormones cortisol (glucocorticoid resistance) and adrenaline. This occurs when prolonged exposure to these hormones causes brain cells to reduce the number and effectiveness of the receptors where these hormones bind: the glucocorticoid receptors that bind cortisol and the β-2 adrenergic receptors that bind adrenaline and noradrenaline. Glucocorticoid resistance makes cells less responsive to cortisol, which impairs negative feedback. Glucocorticoid resistance is involved in many of the diseases associated with toxic stress, such as obesity,

IMMEDIATE RESULTS OF THE STRESS RESPONSE

- Central nervous system: Vigilance, changes in cognition and decision-making
- Cardiopulmonary: Increased respiration, heart rate, blood pressure, oxygenation, and blood flow to brain and skeletal muscles
- Metabolism: Mobilization of stored energy, increased blood sugar, insulin resistance, and shutdown of processes like digestion, growth, and reproduction
- Immune: In early stages (autonomic nervous system), increased inflammation to fight pathogen(s); in later stages, decreased inflammation to rebalance the system

type 2 diabetes, and heart disease.[109,110] Persistently abnormal levels of cortisol and adrenaline alter cell and tissue functions in ways that increase cellular aging and heighten health risks.[10,111-114]

Toxic stress is associated with increased risk for numerous neuropsychiatric disorders, including post-traumatic stress disorder (PTSD), depression, anxiety, substance abuse, attention-deficit/hyperactivity disorder (ADHD), Alzheimer's disease and other dementias, and chronic pain.[39,115-120] While the causes of neuropsychiatric disorders are numerous and complex, changes to the brain's threat response, impulse control, motivation and reward pathways, and pain perception mechanisms are associated with toxic stress and are believed to contribute to these risks. It is important to highlight that although neuropsychiatric disorders are among the most widely recognized manifestations of toxic stress, there is wide variation in which health conditions specific individuals may experience as a result of toxic stress. For example, some experience only immune, metabolic, or endocrine consequences of toxic stress, without any diagnosable neuropsychiatric conditions. Clinical outcomes depend on a complex interplay of predisposing biological factors, genetic and epigenetic makeup, timing and duration of exposures, and buffering factors. These effects can also interact synergistically with those of other toxic exposures (see **LEAD TOXICITY**).

Toxic stress is also associated with structural and functional changes in brain architecture, including many brain regions, such as the amygdala (which governs fear and emotion), hippocampus (memory), prefrontal cortex (executive function), and mesolimbic dopamine system (reward and motivation).[77,121-123] The amygdala, with its role in threat detection, fear, and anxiety, has been measured to be larger and more active in people who exhibit anxiety due to experiencing early childhood adversity. By contrast, the hippocampus and prefrontal cortex have been documented in functional neuroimaging studies to be smaller and less active in individuals with a history of ACEs, and these changes are associated with difficulty with learning, memory, attention, impulse control, and executive functioning.[122,124-135] Further, in toxic stress, the reward system, including the nucleus accumbens, the ventral tegmental area, and the neurochemical receptors for dopamine and noradrenaline (from the SAM system), can change in complex ways.[136-141] One such change is a reduction in dopamine signaling, leading to less intrinsic motivation to perform routine activities, which also become less rewarding, with a predisposition toward mood disorders like depression.[142-152] These changes in reward circuitry may also increase the likelihood of engaging in risky behaviors such as substance use.[142,143,153-157] Because the experiences of reward and motivation can be blunted with early life adversity, it may take more intrinsically motivating factors (such as substance use) to produce a rewarding response. Following childhood adversity, the pain and emotional control circuitry of the brain may be sensitized to respond more

intensely to threatening stimuli, including perceived pain.[158-160] The combination of greater awareness of pain due to changes in specific circuits and hypersensitivity in its perception due to changes in other circuits results in consequences such as increased susceptibility to acute and chronic pain disorders.[161-168]

TOXIC STRESS: IMMUNE AND INFLAMMATORY EFFECTS

Toxic stress is associated with immune dysregulation, which can involve either under-activation or over-activation of components of the immune system. These changes can affect both innate (nonspecific) and acquired (specific) immunity.[175-179]

LEAD TOXICITY

Lead is an example of a specific environmental exposure that interacts with the toxic stress response, in that the effects of lead exposure are more powerful in children who are experiencing toxic stress, and vice versa. Lead exposure disrupts a child's ability to recover from early life stress. Both animal and human studies have identified toxic stress and lead as affecting shared neurobiological systems, including the hypothalamic-pituitary-adrenal (HPA) axis, as well as the frontal cortex and hippocampus (parts of the mesocorticolimbic system). Exposure to lead in early life can result in potentially lifelong alterations in the HPA axis and accentuate physiologic responses to stress.[169]

Exposures to both lead and toxic stressors (like ACEs) together result in enhanced neurotoxicity.[170] Exposure to lead also acts synergistically with stress during pregnancy and early childhood, and is associated with decreased IQ, increased incidence of attention-deficit/hyperactivity disorder (ADHD), antisocial behavior, preterm birth, lower birth weight, and juvenile justice involvement. Higher levels of maternal self-esteem are associated with decreased levels of ADHD and increased cognitive abilities in children, but higher blood lead levels in children reduce that benefit of high maternal self-esteem.[171-174] After pregnant rats were exposed to both lead and stress, their great-grandchildren were found to have residual changes to their stress-related gene expression and biomarkers.[170] In other words, the third generation, which was never exposed to early adversity or lead, exhibited chemical changes to specific genes that are involved in the stress response. This has implications for intergenerational transmission of adversity without the child having experienced direct adversity. (See the next section, **Intergenerational Impacts of Adversity**, for more details.)

A dysregulated immune system is less efficient at fending off pathogens. Most importantly, stress in and of itself often leads to greater vulnerability to infection and autoimmunity (a condition in which the immune system attacks itself, causing disease).[180,181] Toxic stress affects immune cell function, maturation, and reactivity. Chronic stress alters the response to adrenaline and cortisol signaling in the bone marrow, where immune cells are made, resulting in newly born immune monocytes that are proinflammatory and resistant to cortisol's anti-inflammatory signaling.[182-185] Further upstream, stress can also impact the early establishment of gut bacteria, known as the microbiome, which in turn influences the generation of certain immune cells in bone marrow for essential inflammatory responses.[186,187] An individual may also exhibit oversensitivity to the anti-inflammatory properties of cortisol.[188] As a result, dysregulated immune system activity can cause increased likelihood of inflammatory and autoimmune diseases among people with high ACEs and toxic stress, such as arthritis, asthma, food and seasonal allergies, and eczema, as well as increased vulnerability to infectious pathogens.[45,111,189-191]

Altered immune and inflammatory system function is marked by an increase in biomarkers of chronic inflammation, including C-reactive protein (CRP), interleukin-6 (IL-6), and NF-κB.[176,177,192-194] It is also possible to detect elevated levels of virus antibodies, such as to the Epstein-Barr virus, during episodes of high stress. While viruses can exist in the body in a latent, neutral form that does not lead to symptoms because they are maintained in that state by the immune system, stress can suppress the immune system and reactivate these latent viruses, leading to higher levels of active virus, which also triggers the production of antibodies against the virus.[195,196]

Optimal function of the innate and adaptive immune systems is critical for the body to mount a robust defense to new infections like coronavirus disease 2019 (COVID-19).[197] ***Toxic stress physiology may increase risk of contracting or dying from COVID-19***, either through dysregulation of the immune response and/or through increased burden of AAHCs, which may predispose to a more severe COVID-19 disease course (see **COVID-19 AND TOXIC STRESS**). For example, stress is a known trigger of inflammation in the lungs, an organ highly impacted by the the novel coronavirus, SARS-CoV-2.[198-201] Stress-induced lung inflammation can impair respiratory function, similar to that seen in patients with asthma, potentially placing individuals with toxic stress at risk of worse outcomes from COVID-19.[202,203] Beyond the direct influence on lung function, stress can specifically exacerbate the progression of viral pulmonary diseases by impairing innate lung tissue defenses against viral infection.[204-206]

Further, those with toxic stress may also be more susceptible to the health effects of acute or chronic stress. Thus, the biological condition of being stress-sensitized

also increases the risk of stress-related chronic disease exacerbations related to the numerous stressors (e.g., psychosocial, financial, and grief-related) associated with living through the pandemic. For example, acute stress is associated with changes in endothelial cell function, increased arterial stiffness, vessel wall damage, increased blood viscosity, and/or a hypercoagulable state, all of which promote increased risk of blood clots. These changes can result in increased risk for heart attacks and/or strokes, which have been documented to rise significantly in the months following natural disasters such as earthquakes and hurricanes.[207-216]

One study found that people with the highest rates of stress were nearly six times as likely to become infected by cold viruses and over two and a half times as likely to develop clinical symptoms than people with low levels of stress.[197] Children living in stressful situations are approximately one and a half times more prone to fevers than those in low-stress households.[217,218] People who grew up in families of low socioeconomic status, which is also a risk factor for toxic stress, are also more susceptible to viruses that cause respiratory infections.[219,220] People experiencing high levels of stress also receive less protection from influenza vaccines.[221] One recent national study found that, compared to low-stress controls, people with the highest levels of stress are more likely to die from infections overall (67% increased risk), and are especially likely to die from viral infections (114% increased risk), develop pneumonia (83% increased risk), or have bacterial infections (23% increased risk).[222]

Chronic respiratory diseases like emphysema, bronchitis, and asthma all involve inflammation in the lungs, which can be caused by a combination of factors, including stress, cigarette smoking, genetic susceptibility, and environmental exposures.[223,224] The toxic stress response triggers a pro-inflammatory state and also increases the risk of smoking in a dose–response manner, posing cumulative hazards to respiratory health. For adults with an ACE score of five or higher, the likelihood of ever smoking is more than triple the rate for adults with zero ACEs.[225] Due to additional risk factors for poor lung conditions, including environmental exposures, individuals with ACEs are subject to chronic lung diseases more often, demonstrating synergistic interactions between the inflammatory and neurologic consequences of toxic stress.[186] Even when controlling for smoking behavior, adults with five or more ACEs are more than twice as likely to develop chronic obstructive pulmonary disease (COPD), one of the leading causes of death in the US.[226-228]

Children with four or more ACEs face a 1.7-fold increased risk of asthma, with Latinx children exhibiting 4.5-fold increased risk, compared to those with zero ACEs.[229] Asthma arises from a diverse interplay of factors, involving the gut microbiome, immune and inflammatory system alterations, environmental exposures (see **EARLY ADVERSITY AND EXPOSURE TO POLLUTION**), acute stressors, and changes to the stress

response system, including to key receptors.[202,230,231] At the molecular level, early adversity is associated with lower concentrations of the β-2 adrenergic receptor, which is the molecular target of a first-line medication for asthma exacerbations called albuterol, and lower concentrations of the glucocorticoid receptor, targeted by steroid treatments like prednisone. Due to the receptors' downregulation, these standard asthma treatments may be less effective in individuals with ACEs (see **Primary and Secondary Prevention Strategies in Healthcare** and **Tertiary Prevention Strategies in Healthcare**, in Part II, for more information).[230]

Chronic inflammation may heighten the risk of cancer through multiple mechanisms, including increasing the DNA mutation rate and increasing new blood vessel growth (angiogenesis), which funnels nutrients to tumors. Once a cancer has developed, chronic inflammation can promote its transformation and spread by interfering with normal anti-tumor mechanisms, increasing cytokine production, and creating cancer-protective micro-environments.[237-240] Chronic inflammation

EARLY ADVERSITY AND EXPOSURE TO POLLUTION

During the earliest years of life, the lungs are most sensitive to environmental pollutants. Prolonged or extreme exposure to air pollutants can affect pulmonary development, impacting health outcomes throughout childhood and beyond. As the tissues develop, the lungs are especially vulnerable to exposure to particulate matter, such as from smoke, traffic-related air pollution (TRAP), or high concentrations of dust. Exposure to ACEs and the associated dysregulation of the immune system involved in toxic stress can combine with breathing polluted air to exacerbate negative asthma-related outcomes. For example, one study demonstrated that children who lived among high levels of TRAP were at 1.5 times greater risk of developing asthma, but only if their parents reported a high degree of stress, suggesting a concomitant immunological vulnerability from early adversity.[232,233] In childhood, air pollutants and stress interactions are associated with changes in specific inflammatory mediators that can be related to worsened asthma outcomes, including interleukin-5, IgE (the allergic-type antibodies), and eosinophil counts (allergic-type immune cells).[234]

As another example, in utero exposure to both stress and air pollution can increase oxidative stress, which may affect the development of the fetal lungs, including increasing airway inflammation and adverse simplification of the normally complex structure.[235,236] In fact, an increased risk of asthma was found in children co-exposed in utero to fine particulate matter ($PM_{2.5}$) and maternal stress (OR 1.15; 95% CI, 1.03-1.26) during the phase of lung development when many of the peripheral airways important in asthma develop (canalicular phase).

and increased generation of oxygen radicals (also known as oxidative stress), in combination with failure of genetic regulatory mechanisms, can also interfere with the success of some cancer treatments.[237-240] Many cancers are caused by underlying inflammatory changes. For example, studies estimate that 18% of cancers are linked to chronic infection, 30% to smoking, and 35% to dietary factors (14% to 20% specifically to obesity).[241-244] Particulates and carcinogens from cigarette smoke, and other environmental hazards such as asbestos and pollution, lead to chronic inflammation in the lungs and other places in the body.[245] There is growing evidence, as well, that exposure to nicotine during pregnancy or infancy leads to accelerated cellular aging, through epigenetic changes.[246]

TOXIC STRESS: ENDOCRINE AND METABOLIC EFFECTS

The endocrine system consists of a finely tuned internal communications network driven by hormone production, transportation, and negative feedback loops via a network of glands and blood vessels throughout the body. Collectively, hormones coordinate and drive the most essential functions, including metabolism, growth and development, reproduction, and responses to stress, injury, and environmental factors. Stress, infections, disruptions to metabolic activity, and many other circumstances can trigger and exacerbate endocrine disorders, potentially leading to abnormal growth patterns, weight gain or loss, early or delayed puberty, loss of bone mass, reproductive problems, and dysregulation of metabolic processes like energy storage and use, among others.

Metabolic syndrome describes a clustering of health conditions, including high blood pressure, high fasting blood sugar, insulin resistance, excess abdominal fat, abnormal cholesterol, or abnormal triglyceride levels, and it is more likely to occur in people who have experienced adversity during childhood.[247,248] Metabolic syndrome is, in turn, related to increased risk for cardiovascular disease, including heart attacks and ischemic heart disease; cerebrovascular disease, including stroke; type 2 diabetes; and obesity.[249-251] Notably, of all the health costs associated with AAHCs studied to date, cardiovascular disease comprises the greatest share.[63,64] Toxic-stress-related inflammation is one cause for increased risk of metabolic syndrome after adversity. Elevation of one marker of inflammation, IL-6, is correlated with risk of heart attack (myocardial infarction). One study found that people in the highest 25% of IL-6 expression have a 2.3-fold increased rate of heart attack, compared with the lowest 25%.[252] In other studies, people with the highest levels of the inflammatory marker CRP are at 4.4-fold increased risk for heart failure, heart disease, and death, while tumor necrosis factor-alpha (TNF-α) levels are associated with increased risk for heart failure, heart attacks, and small-

vessel disease.[250,251,253-255] Cardiometabolic risk is also increased by smoking, lower physical activity, increased body mass index, and increased blood pressure. The first three of these factors are independently associated with a history of ACEs in a dose–response fashion, further increasing cardiometabolic risk for those with toxic stress.[2,3,13,256,257]

Toxic stress also increases risk for obesity and for being overweight.[3] Changes in brain reward signaling pathways, as well as metabolic hormones which govern feeding and hunger cues, may predispose to overconsumption of high-fat, high-sugar foods.[113,258,259] Leptin is a hormone that helps signal satiety or fullness.[260] During the fight-flight-or-freeze stress response, leptin is released acutely. However, following chronic stress, leptin resistance occurs, and the body may not appropriately signal fullness (satiety) after a meal, and this may contribute to overeating.[259,261,262] The production of other appetite- and metabolism-regulating hormones, including neuropeptide Y and ghrelin, has also been measured to be altered following adversity in ways that promote cardiometabolic risk.[263-268]

Type 2 diabetes is caused by dysregulated insulin production by the pancreas and reduced sensitivity (insulin resistance) exhibited by cells throughout the body and brain. Toxic stress can increase risk for these outcomes. Prenatal exposure to major stressors may result in impaired regulation of glucose metabolism.[269-273] Early adversity can reduce the production of insulin, a key hormone needed to regulate glucose levels, resulting in abnormalities in insulin and glucose metabolism.[113,274-278] Moreover, prolonged exposure to glucocorticoids can result in whole-body insulin resistance.[279-283] Stress may even change patterns of insulin secretion intergenerationally, leading subsequent generations to be more susceptible to diabetes.[113,117,269,271] Insulin resistance has been identified as a potential unifying factor for certain mental and physical health problems in individuals who experienced early life adversity. Lipid metabolism can also be disrupted by toxic stress, further increasing metabolic risk—and these changes can be transmitted to future generations.[284,285]

Kidney disease is also a major source of mortality in the US, affecting more than one in seven (37 million) people. People with four or more ACEs are at 1.7-fold increased risk of developing kidney disease (relative to those with zero ACEs).[16,286] Converging risk factors include heart disease, obesity, diabetes, and high blood pressure.[286-289] Several studies have suggested a convergent mechanism for cardiovascular and kidney disease through dysregulation of endothelin-1, which plays a role in blood pressure and arterial stiffness and is activated in response to stress.[290-298]

TOXIC STRESS: EPIGENETIC AND GENETIC EFFECTS

Adversity in early life is associated with changes in how DNA is read and maintained, broadly called the epigenetic landscape, and it is capable of altering the regulation of gene expression that governs multiple biological processes.[299-301] A diverse set of factors attached to DNA, called epigenetic markers, can alter the

BIOMARKERS ASSOCIATED WITH TOXIC STRESS

While there currently exist no widely agreed-upon clinical diagnostic criteria for toxic stress, a number of biomarkers associated with neuro-endocrine-immune-metabolic disruption are under investigation.[332-334] Although the definition continues to be refined, in broad terms, a **biomarker** is "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers."[335] Though this research is still nascent, the biomarkers below have been associated with toxic stress and/or ACEs and may become clues or targets to identify patients at risk for toxic stress and associated poor health outcomes. These biomarkers and the clinical pathways they inform may also offer insight into potential therapeutic targets and precision medicine treatments to ameliorate the impact of toxic stress on health and well-being.[336,337]

Markers of inflammation

> Soluble urokinase plasminogen activator receptor (suPAR); interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α); C-reactive protein (CRP)[194,338-342]

Markers of stress, stress reactivity

> Cortisol: both higher and lower levels of cortisol have been reported in toxic stress[343-346]

Markers of altered metabolism

> Leptin[259,261,341,347]; ghrelin[263,264]; neuropeptide-Y (NPY)[265-268]

> Mitochondrial DNA accumulation[348,349]

Marker of cellular aging

> Telomere length[299,350]

Markers of epigenetic regulation

> Various, including methylation of the serotonin promoter and FκBP-5[313,316,351-353]

While many potential biomarkers for toxic stress have been proposed, few have been fully validated. Fewer have been translated into successful models for use in diagnosis, risk stratification, or assessing treatment efficacy modalities in treating toxic stress or its health complications or subtypes (i.e., metabolic, immune, neuropsychiatric, or endocrine).

way in which genes are transcribed in response to lived experiences; they include DNA methylation, histone post-translational modifications, and small noncoding RNAs.[302,303] Epigenetic markers can arise from environmental influences or may be passed from parent to child via the sperm and egg (paternal and maternal germ lines). Studies using animal models on the effects of early life stress on maternal separation, maternal care quality, and exposure to stressors demonstrate how epigenetic changes may affect offspring behavior and health throughout life.[304-307]

For people with toxic stress, aging faster is not a metaphor; those with six or more ACEs live, on average, almost 20 years less than those with none.

Recent studies suggest that childhood adversity is associated with premature cellular aging, which is measured by proxies such as shortened telomeres and an advanced epigenetic clock (a combination of epigenetic markers that indicate the biological age of cells). Telomeres are regions at the ends of DNA strands that protect them from degradation, and because telomeres are shortened over time, they act as a countdown clock to cellular senescence and death.[301,308] As cells age, their functioning declines.[309] Stress, especially in early and middle childhood, leads to shortened telomeres and premature cellular aging.[12,310-316] Accelerated cellular aging as a component of toxic stress physiology may lead to higher rates of cancer, diabetes, rheumatoid arthritis, lupus, and Alzheimer's disease and other dementias.[317-323] Toxic stress is associated with cognitive decline and other markers of aging.[10,249] For people with toxic stress, aging faster is not a metaphor; those with six or more ACEs live, on average, almost 20 years less than those with none.[29]

It is also known that, in addition to the 10 ACEs, there are other risk factors for toxic stress, such as poverty and racism, that exacerbate these impacts. For example, the top 1% of earners live an average of 14.6 years longer than the bottom 1%; further, White Americans live approximately five years longer than Black Americans, and about 80% of this difference can be attributed to socioeconomic factors.[29,324-328]

Epigenetic changes are driven by life experiences, both positive and negative. While initially thought to be permanent, recent studies provide examples that building resilience and targeted treatments can reverse or prevent negative epigenetic changes resulting from childhood adversity, as well as subsequent biological risks.[329-331] This unique capacity for reversibility of some epigenetic changes offers some hope for epigenetic processes as targets for toxic-stress-specific buffering interventions.

While many potential biomarkers for toxic stress have been proposed, few have been fully validated. Fewer have been translated into successful models for use in diagnosis, risk stratification, or assessing treatment efficacy modalities in treating toxic stress or its health complications or subtypes (i.e., metabolic, immune, neuropsychiatric, or endocrine).

The current status of biological impacts of interventions to regulate toxic stress physiology is presented in **Tertiary Prevention Strategies in Healthcare** (in Part II), but much work remains to be done in these domains.

COVID-19 AND TOXIC STRESS

Public anxiety about the risk and consequences of the novel coronavirus disease 2019 (COVID-19), compounded by economic distress due to lost wages, employment, and financial assets, fear and grief, coupled with mass school closures and wide-scale physical distancing measures, represent a "perfect storm" for stress-related morbidity and mortality.

Widespread infectious disease outbreaks, natural disasters, economic downturns, and other crises have in common a number of well-documented short- and long-term health impacts, including increased cardiovascular, metabolic, immunologic, and neuropsychiatric risk. These risks accrue through a variety of mechanisms, including:

- Disruption of access to healthcare, including medications;
- Disruption of access to resources needed for health maintenance, such as nutritious foods and safe places to exercise;
- The direct effect of the inciting event driving an overactivity of the biological stress response, leading to neurologic, endocrine, immunologic, and genetic regulatory disruptions, with
  - increased incidence of ACEs and other risk factors for toxic stress, and
  - decreased sources of buffering care.

The conditions imposed by the COVID-19 pandemic have placed families at greater risk for ACEs and other risk factors for toxic stress; decreased access to buffering sources of support such as schools and community-based organizations; and downstream health impacts.[354-356]

At a population level, the impacts of crises also tends to worsen social inequities and health disparities. These health and social impacts particularly affect those with higher baseline vulnerability, including individuals with a history of adversity, those with lower incomes and education, those more vulnerable to job loss, housing insecurity, food insecurity, and poverty, as well as those with underlying chronic health conditions, disabilities, and older age.[212,214,216,357-403] Fear-related thoughts and behaviors can both worsen pandemic spread, as well as increase the short- and long-term health risks, because fear interferes with cognitive processing and executive functioning. For example, in West Africa, during the Ebola crisis (2013–2016), fear-related behaviors were implicated in speeding up the spread of Ebola; preventing treatment; enhancing the spread of malaria, tuberculosis, and HIV; disrupting care and leading to maternal and neonatal mortality; magnifying stigma; and accelerating negative economic effects.[386-388]

The health impacts of prior infectious disease outbreaks, natural disasters, and economic downturns include:

- **Increased heart attack and stroke.** After the Hanshin-Awaji

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earthquake, there was a threefold increase in myocardial infarctions and a doubling of the incidence of stroke in those living close to the epicenter.[214,376]

- More than two years after Hurricane Katrina, survivors were found to have a threefold increase in myocardial infarction rates, relative to pre-Katrina rates.[216] Heart disease was also increased (15% greater) at one year post-Katrina.[397]
- Mechanistically, "acute stress can trigger cardiovascular events predominantly through sympathetic nervous activation and potentiation of acute risk factors (blood pressure increase, endothelial cell dysfunction, increased blood viscosity, and platelet and hemostatic activation)."[376]
- **Blood pressure increases.** Major disasters can produce systolic blood pressure increases of 5–25 mmHg for 1–6 months thereafter, particularly for those with risk factors (older age, chronic kidney disease, obesity, metabolic syndrome, diabetes), and only resolve "when the disrupted behavioral and biological circadian rhythm is restored."[212]
- **COPD and asthma exacerbations.** In the wake of the 2008 financial crisis, 11.5% more COPD exacerbations and 14.1% more hospitalizations resulted.[372] Acute and chronic stress are well known to lead to increased rates of asthma exacerbation. "Stress-induced asthma may be explained by epigenetic, immunological and neuro-mediator mechanisms. Stress has a neuro-immune modulating effect, leading to bronchoconstriction. One study reports half of new-onset asthma in war is due to stress, especially PTSD."[378] PTSD can lead to long-lasting alteration of the immune system, including dysfunction of regulatory T cells and switching to an IgE antibody profile, making asthma more likely.[378]
- **Poorer diabetes outcomes.** Hemoglobin A1c levels rose from 7.7% to 8.3% in diabetes patients in a safety net system, many without insurance, who did not receive continuous diabetes care for about a year, when measured 6–16 months after Hurricane Katrina.[379] Seniors with diabetes who lived in a county highly impacted by Hurricanes Katrina and Rita (N = 170,138), compared to those who did not (N = 170,138), had a nearly 40% higher all-cause mortality risk in the one month following the disasters, which diminished over the subsequent nine years, but was maintained at 5.6% at nine years.[397]
- Nephritis-related death was 27% greater at one year post-Katrina in survivors.[397]
- **Immune system dysregulation can result**, leading to increased secondary viral and other infectious disease susceptibility and poorer oral health.[212,366,377,380,381]
- **New-onset or recurrent mental and behavioral health conditions**,

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especially in those with longer duration of isolation, inadequate information, and/or inadequate supplies:[216,357-375,382,383]

- Depression, suicidality, completed suicides, by as much as 35 to 57%[369]
- Anxiety
- PTSD—about one-third of young children (5 to 8 years) who lived through the Great East Japan Earthquake had symptoms of PTSD two years later[360]
- Acute grief
- Obsessive-compulsive disorder
- Specific phobias
- Substance use—increased alcohol dependence were reported three years after quarantine for SARS.[384,385]

› **Poorer birth outcomes**, such as preterm birth, intrauterine growth restriction, low birth weight, and other intergenerational health and social risks:

- Women who were pregnant during or just after the 1998 Quebec ice storm had activation of their stress response and genetic regulatory systems in ways that were transmitted to their offspring. For instance, their children were found to have one-third of a standard deviation lower birth lengths,[389] and altered gene expression mechanisms into adolescence in ways that altered their immune and inflammatory profiles.[390,391] In adolescence, these children had altered energy and protein metabolism patterns that promoted lifelong risk for diabetes and obesity.[392] Cognitive and IQ-related deficits were also seen.[393]
- After the 2008 earthquake in Wenchuan, China, in births a year after the earthquake, the preterm birth rate went up by 130%, the low birth weight rate went up by 135%, and the rate of birth defects went up by 114%, as compared to the year prior.[394]
- Following the 1918 flu pandemic, children of infected mothers were up to 15% less likely to graduate from high school. Wages were 5–9% lower. Socioeconomic status was substantially reduced, and the likelihood of being poor rose as much as 15% compared with other cohorts.[395]

› **Risk for increased household violence.**[396]

The burden of these kinds of acute increases in ACEs, toxic stress, and AAHCs has been even more pronounced during the COVID-19 pandemic. In the first six months of the pandemic, hospitalization rates skewed higher among people with preexisting conditions. For example, individuals with diabetes, hypertension, or moderate obesity were three times more likely to be hospitalized than people without these respective diagnoses.[404] According to one study by the CDC, the mortality rate for people with underlying health conditions, including many AAHCs, was 12 times higher than for people without underlying health conditions.[405]