Intergenerational Transmission of Adversity

Parental Adverse Childhood Experiences (ACEs) and toxic stress can affect the health of subsequent generations—with effects transmitted from parent to child and even to grandchild. Both protective factors and risks for poor health can accrue over generations through innate and experiential factors. To successfully mitigate the impact of ACEs and toxic stress on health and well-being, we must understand the mechanisms by which adversity and its harmful consequences can be transmitted across generations. While the previous sections of this report detail how toxic stress may lead to poor health outcomes, this section reviews the literature linking parental and caregiver ACEs and toxic stress with the health and well-being of their children.

DEFINITION OF INTERGENERATIONAL TRANSMISSION

Intergenerational transmission of toxic stress occurs when adverse experiences alter parental biology or behavior in ways that affect the development and health of their children. This includes changes to parental and child neuro-endocrine-immune-metabolic and genetic/genetic regulatory function, in ways that matter for pre-conception health, and also influence pregnancy, birth, infant, and child health outcomes. Parenting behaviors, positive experiences, societal factors, and historical traumas also influence the way that health risks are passed on from parent to child.

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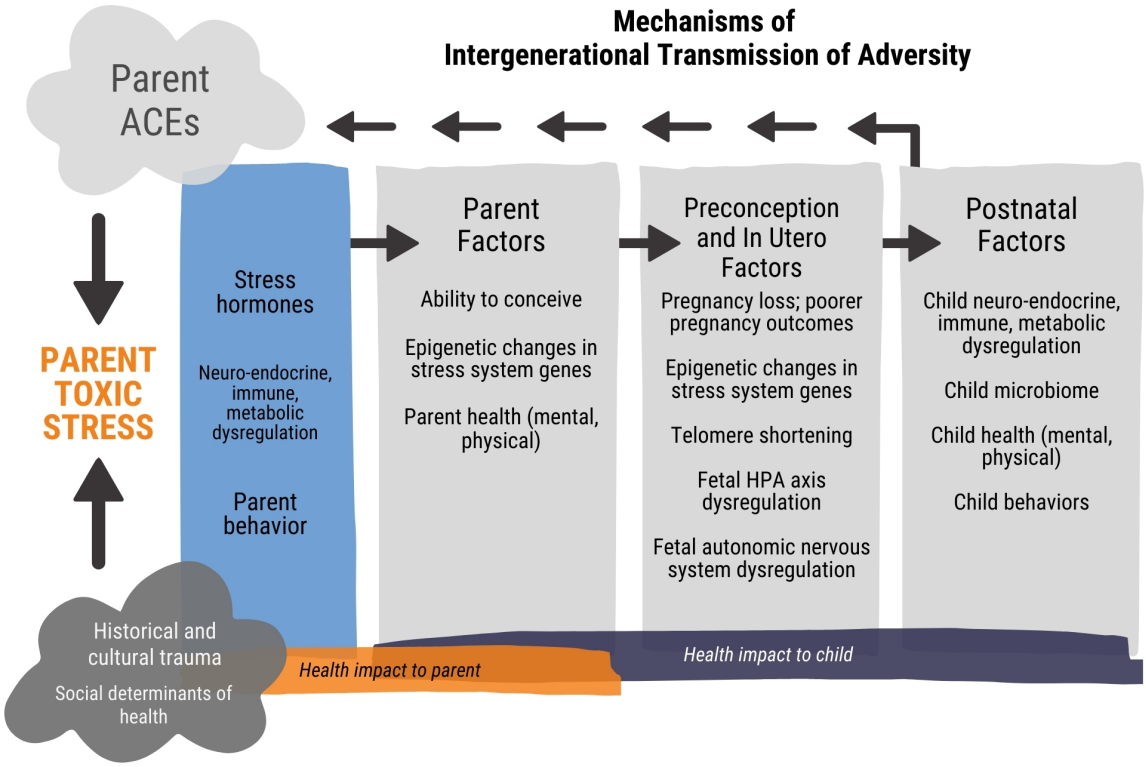

Figure 6. *Parental ACEs and toxic stress lead to multiple biological changes that may impact the health of their children.*

Children born to parents with high ACE scores are more likely to have neuropsychiatric, behavioral, and physical health problems, including sleep disturbances, anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), asthma, autism, schizophrenia, and post-traumatic stress disorder (PTSD), among others.[302,303,406-427] Over the past several decades, researchers have begun to elucidate the mechanisms by which childhood adversity leads to poorer health and life outcomes.[20,275,413,422,424,428-432] Science points to the toxic stress response, or prolonged activation of the biological stress response and associated disruption of neuro-endocrine-immune-metabolic, and genetic regulatory functioning, as key mechanisms by which early adversity leads to increased risk of disease and early death across the life course and for future generations. Parental ACEs are associated with neuropsychiatric, endocrine, immune, and metabolic dysregulation in their offspring (**Figure 6**).[414,433] Unfortunately, these pathways have been largely under-recognized and under-addressed in clinical practice and policy.

Parental ACEs and other life stressors can affect their offspring both directly, via disruptions in caregiver stress hormones, neuro-endocrine-immune-metabolic

function, and epigenetics, and indirectly, via caregiver behavior, societal factors, and historical and cultural trauma. These topics and their consequences for parental health are discussed in more depth in the previous section, T**he Biology of Toxic Stress**, and will be addressed here specifically in the context of the intergenerational transmission of toxic stress. Understanding the mechanisms by which this transmission occurs will allow clinicians, educators, researchers, and policymakers to develop and use specific strategies to address these issues.[413-416]

While this review focuses on the potential risks of ACEs across generations, it is important to recognize that (1) some stressful experiences are healthy, and the studies presented here are focusing on repeated, prolonged, or severe stress;[6] (2) many of these pathways may represent flexible adaptations to help prepare the next generation for the harsh world experienced by the caregiver;[434] (3) resilience can also be passed to the next generation through potentially many of the same pathways;[434,435] and (4) many, if not all, of these pathways can be mitigated or healed with supportive caregiving and other interventions (see later sections of this report, including **Tertiary Prevention Strategies in Healthcare** in Part II).

DIRECT IMPACTS OF PARENTAL TOXIC STRESS PHYSIOLOGY: STRESS HORMONES

In their summary of evidence on the developmental origins of disease, Keenan and colleagues discussed the relationship of preconception stress exposure to health disparities in obstetrics and offspring outcomes.[436] They posited that pregnancy health depends on maternal health prior to conception. They cited strong evidence across species for negative effects of maternal prenatal stress on the developing fetus and on subsequent development throughout childhood. Furthermore, while it is still debated by the field, the authors noted that the association between prenatal stress and offspring neurodevelopment may be due largely to pre-conception stress exposures.

Ability to conceive

ACEs and toxic stress affect the very first steps of childbearing by altering pubertal timing, age of menarche, menstrual regularity, egg and sperm quality, and ultimately, the ability to become pregnant.[6,437-440] High stress levels are associated with reduced odds of conception.[436,437,441] This has been tied directly to increased activity of the hypothalamic–pituitary–adrenal (HPA) axis, which regulates stress reactivity, suppressing the normal function of reproductive pathways.[442] Higher levels of corticotropin-releasing hormone (CRH) and glucocorticoids associated with stress (such as the hormone cortisol) suppress the normal function of the gonadotropin-releasing hormone (GnRH), resulting in lack of ovulation or egg

production in women (anovulation). For women, but not men, higher perceived pre-conception stress is associated with slight reductions in peak fertility (fecundability).[441]

Pregnancy loss

Significant stress in the pre-conception and early pregnancy periods has been associated with an increased risk for pregnancy loss.[430,443-446] In the original Kaiser Permanente/Centers for Disease Control and Prevention (CDC) ACE Study, maternal ACE scores of five or more were associated with an 80% increased risk of fetal demise for pregnant adolescents.[447] A study of 2,795 adult women found that an ACE score of three or more was associated with twice the risk of miscarriage (RR 95% CI 1.25-3.22).[448] Physical abuse and sexual abuse were each individually also associated with increased risk. One meta-analysis of studies found that a history of psychological stress was associated with a 1.4-fold risk of miscarriage.[445] Frazier and colleagues detailed ways in which cortisol, other aspects of the HPA axis, and immune factors related to stress may increase risk for miscarriage.[444]

Preterm birth and low birth weight

ACEs, childhood adversity, cumulative stress exposure, and allostatic load (whole-body adaptation to stress through changes in neuroendocrine, immune, metabolic, and cardiovascular functioning)[449] during pregnancy are associated with increased risk for low birth weight and preterm birth, which are also risk factors for various adulthood diseases.[429,446,450-454] Women with an ACE score of two or more have a 2.1-fold increased risk of preterm birth compared to those with no ACEs.[429] Pregnant mothers who had experienced childhood sexual abuse were found to have increased hospitalizations during pregnancy, premature contractions, cervical insufficiency, and premature birth.[431] Exposure to intimate partner violence (IPV) has also been associated with vaginal bleeding, preterm birth, and perinatal death.[455,456]

Elevated maternal cortisol concentrations in the bloodstream give rise to elevated cortisol levels in the placenta and amniotic sac, which, in turn, may impair the development of the baby, leading to increased risk of preterm birth and lower birth weight.[457,458] In addition, lower birth weight was found in one study to be correlated with increased infant fear and distress responses.[457]

Higher levels of the stress hormone norepinephrine (also known as noradrenaline) in maternal urine, representing overactivation of the fight-flight-or-freeze system, were associated with increased risk for spontaneous preterm delivery.[459] Another study found associations between maternal childhood hardship, immune system dysregulation, high blood pressure, obesity, and preterm delivery.[460]

Preterm birth is more common in Black women and contributes to an infant

mortality rate twice as high among Black women as among White women.[461] Known risk factors, including socioeconomic status, genetics, and health behaviors, do not fully account for this racial disparity.[461] Psychological stress, including the stress of experiencing racial discrimination, may contribute to this increased risk for preterm birth and higher mortality rates.[461]

Infant HPA axis

Perinatal adversity and parental stress before and during pregnancy may have significant effects on the subsequent functioning of the child's HPA axis, which, in part, controls stress reactivity.[266,462,463] The placenta plays an important role in regulating the transmission of cortisol, a major stress hormone, between the mother and fetus, and may protect the fetus from normal variations in maternal cortisol levels.[427] However, high levels of maternal cortisol may alter these regulatory mechanisms of the placenta, leading to negative impacts on fetal development.[427] Cortisol levels in tissues that surround the growing fetus, like the placenta and amnion, have been found to predict the stress response of the child after birth. For example, higher levels of cortisol in-utero predicted higher pre-stress cortisol values and a dysregulated response to stress exposure in infants.[464,465] In a study by Moog and colleagues, maternal childhood trauma (that is, trauma experienced by the mother when she was a child) was associated with increased placental production of the stress hormone, CRH.[466] Dysregulated infant cortisol responses to a stressor have been associated with maternal stress and high maternal cortisol levels.[464,467-469] These effects produce what can be conceptualized as a maladaptive HPA axis, with elevated cortisol levels both prior to stress and after it abates, coupled with blunted levels during stress.

Timing

The consequences of fetal stress exposure depend on its timing and duration. For example, stress exposure early in pregnancy is associated with increased likelihood of pregnancy loss, while stress exposure later in pregnancy has been associated with increased risk of low birth weight.[413] These effects appear to be species- and sex-specific. There may be critical windows of neurological, endocrine, and immune development affected by stress.

Buffering factors and timing

A meta-analysis of 39 studies evaluating the effects of psychosocial interventions to reduce the effects of stress on fertility rates among couples experiencing infertility found a robust effect for both psychological outcomes (including depression, anxiety and marital function) and fertility rates.[470]

Social support during pregnancy and after birth may play an important role in

mitigating the impact of stress hormones on offspring. A study of 243 mother-infant dyads found that maternal ACEs were associated with maternal HPA function during pregnancy and infant HPA reactivity. However, many of their findings were observed when levels of social support were low.[454] This study also identified different trimester effects, where social support in early pregnancy moderated the impact on the pattern of maternal cortisol secretion, while support in later pregnancy impacted the amount of cortisol.[454]

DIRECT IMPACTS OF PARENTAL TOXIC STRESS PHYSIOLOGY: EPIGENETICS

Each cell in our body contains our genetic code, which consists of approximately 30,000 genes and act as a map for cell functioning. Genes, however, do not decide when they are read. Instead, they are controlled by chemical "on-off" switches: upstream elements that regulate gene expression. Epigenetics is the process by which particular environmental influences can move a particular switch to an "on" or "off" position. Through this mechanism of epigenetics, our experiences—good and bad—can change how genes are read and transcribed into proteins without altering the gene sequence. Epigenetic changes may be transmitted to the next generation, and include DNA methylation, histone post-translational modifications, and small noncoding RNAs.[302] Intergenerational transmission of epigenetic changes may occur through preconception changes to the egg or sperm (germ lines) that are passed on to the offspring or as in-utero changes directly to the fetal DNA.[433] (Of note, germ lines are formed at different times. Whereas females begin producing eggs from their time as a four-week-old embryo, still in their mother's womb, males begin producing sperm after puberty. Hence, the impact of the environment on the germ lines may be different by sex.)

Large-scale tragedies such as the Dutch Hunger Winter and the Holocaust altered epigenetics for survivors and their offspring in ways that are detectable decades and generations later.[471] In both animal and human studies, these methylation changes have been associated with lower birth weight, altered metabolic activity, and changes in cortisol levels and glucocorticoid (cortisol) receptor sensitivity, as well as increased health risks throughout life, including psychiatric and neurodevelopmental disorders.[302,414,433,472-476] Paternal and maternal adversity and stress have been associated with epigenetic changes in their offspring, including changes to genes encoding proteins that control glucocorticoid receptor function, factors that control glucose and lipid homeostasis, and the regulation of telomere length.[303,351,413,414,468,476-481] (Telomeres are parts of chromosomes that protect them from degradation. Shorter telomere length has been associated with premature cellular aging.) Given the complexities of conducting controlled adversity-related studies

in humans, the most compelling research on epigenetic transmission involves animals. However, research on epigenetic patterns in humans is advancing quickly, including prospective, multi-generational studies.[475]

Paternal impact

Much of the animal epigenetics research deals specifically with male sperm and male offspring. This focus helps pinpoint effects to epigenetics, since it eliminates the profound contributions of fetal experiences, including from environmental factors and maternal behaviors, when females were studied. This research has found that epigenetics is a critical pathway by which paternal ACEs and stress can affect offspring. In mice, paternal stress (via fear conditioning and separation from their mother) has been associated with changes to DNA methylation of stress regulatory genes in sperm.[302] Male offspring born to stressed adult male rats (by forced swimming) had increased anxiety behavior, increased stress hormone levels, and epigenetic changes in a glucocorticoid-receptor gene, when compared to offspring born to non-stressed male rats.[472] Animal models have also found early traumatic stress may alter microRNA expression in sperm, influencing offspring HPA axis, neurodevelopment, and subsequent metabolic and behavioral outcomes.[302,414,433,473,482]

Placenta

Emerging evidence suggests that the placenta is highly susceptible to maternal distress prior to and during pregnancy.[483] The placenta can act as a "filter" to decrease the amount of cortisol that passes from mother to fetus. This may occur through epigenetic changes to the placental enzymes that convert cortisol into either an active or an inactive form. Methylation patterns of these genes have been found to have a significant effect on the baby's birth weight.[484] Epigenetic changes associated with pre-conception trauma in parents may also affect the DNA in eggs and sperm, altering the shared genomes of the fetus and placenta, and potentially impacting their development and interactions.[475] Changes in the genetic and epigenetic code of eggs and sperm alter the DNA blueprint for a child during development, influencing health throughout life.

Gene methylation

Fetal exposure to inflammatory proteins and cortisol has been associated with epigenetic changes (miRNA expression and DNA methylation) in the fetal brain, including alterations in neurotransmitter levels, cell survival, growth of new brain cells, connections between brain cells, and myelination (a process by which a fatty sheath surrounds axons of neurons and speeds up signaling).[433] (See the prior section, **The Biology of Toxic Stress**, for a discussion of how excessive inflammation, such as exposure to inflammatory messenger proteins during fetal

life, has adverse effects on adult health.) The methylation patterns of several genes, including genes for a glucocorticoid receptor, a serotonin transporter, T cell immune function, brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), and a catecholamine regulator, have all been connected to stress and health outcomes in offspring.[303,351,413,414,477-479] For example, a recent study found maternal depression was associated with methylation of a fetal cortisol receptor gene and infant cortisol responses, suggesting a mechanism for offspring HPA axis programming.[468]

Grandparents

One of the more provocative studies in the field of stress physiology involved male mice conditioned to fear certain smells by pairing these scents with a shock. Dias and colleagues found that offspring of the odor-fear-conditioned male mice were extremely sensitive to the odor, despite never having met their fathers and never having been odor-fear-conditioned themselves. Strikingly, the grandchildren of the fear-conditioned mice also experienced extreme odor sensitivity. In other words, fear conditioning was passed from grandfather to father to grandson. The researchers found this intergenerational transmission to be associated with epigenetic changes of a gene linked to the sense of smell.[485]

Telomere length

Epigenetic modifications of DNA continue to affect health and development after birth. Telomeres are non-coding sequences of DNA found at the end of each chromosome that protect the chromosome from degradation. Shorter telomere length has been associated with premature cellular aging, and has been correlated with high chronic stress, though with some mixed results. Some studies have suggested that maternal stress may impact fetal telomere length, suggesting another pathway for intergenerational transmission of toxic stress. Higher maternal prenatal stress has been associated with significantly shorter telomeres in those mothers' newborns, compared to newborns born to mothers with low prenatal stress.[480,481] Likewise, pre-pregnancy health risks like smoking, elevated body mass index (BMI), and low family support are associated with shorter telomeres in newborns.[486] A recent study by Esteves and colleagues found high maternal ACEs to be associated with shorter telomere length in their infants, as well as with increased externalizing behavioral problems at age 18 months. These findings were not explained by maternal postpartum depression or by prenatal stress.[487]

A growing body of research is finding that interventions such as supportive parenting, aerobic exercise, and nutrition may reduce stress and protect or even lengthen telomeres.[488-491] For example, Child-Parent Psychotherapy (CPP) has been shown to protect against telomere shortening associated with trauma, suggesting

the intervention slowed, stopped, and for some children reversed the cellular "wear and tear" of early adversity.[492]

OFFSPRING NEURO-ENDOCRINE-IMMUNE-METABOLIC DYSREGULATION

ACEs and toxic stress are risk factors for a number of health conditions, as detailed in previous sections. Health issues in parents are known risk factors for similar health issues in their offspring. This section will focus on how caregiver stress can lead to offspring neurological-endocrine-immune-metabolic dysregulation, leading to increased risk for offspring poor health.

Neurologic and psychiatric health

Maternal stress and associated endocrine and immune system dysfunction may alter fetal brain structures involved in the stress response, including the hippocampus and amygdala, preprogramming the child for greater stress reactivity.[462,493] ACEs are a risk factor for maternal anxiety and depression, which, in turn, increase the risk of a child having mental health conditions like antisocial conduct disorder or depression.[417,494-498] Haynes and colleagues found that having a caregiver with four or more ACEs was a greater risk factor for a child's developing depression or anxiety (aOR 3.0) than having a caregiver with depression or anxiety without ACEs (aOR 2.2).[499]

Autonomic nervous system

ACEs and the associated fight-flight-or-freeze response can lead to prolonged activation of the autonomic nervous system. Markers for activation of the sympathetic nervous system (SNS) include elevated heart rate, salivary alpha amylase, and norepinephrine and epinephrine levels. The parasympathetic nervous system (PNS) counteracts the fight-flight-or-freeze response and is associated with recovery from stress. Measuring the activity of the PNS is more difficult than that of the SNS; however, markers such as respiratory sinus arrhythmia (RSA) and heart rate variability are often used, with or without association with breathing.

One study found that infants born to mothers with fearful temperaments and anxiety had higher tonic heart rates at age four months, which predicted a more fearful temperament at two and a half years.500 Higher infant heart rate reactivity and less heart rate recovery after a stressful experience at age four months also predicted a more fearful temperament during infancy and toddlerhood. This finding suggests that autonomic hyperarousal can be passed from mother to child early in infancy before learned behavior can occur. Gray and colleagues found that high maternal ACEs were associated with lower infant RSA (suggesting

lower parasympathetic activity and/or increased stress activation in the infant), while prenatal stress was associated with an infant's failure to recover following a stressor.[501] Sex differences were observed, with higher RSA in boys and lower RSA in girls. Lower RSA has been linked to increased risk for stress-related disorders, including cardiovascular disease, depression, anxiety, and PTSD.[502]

Endocrine/metabolic health

Health impacts of parental stress and poor health extend beyond perinatal effects into adulthood. For example, children of parents exposed in utero to the Dutch Hunger Winter of 1944 had higher BMIs and poorer heath than those born to unexposed parents.[272,503] One recent study found that each maternal ACE successively increased the likelihood of child health problems, with children of mothers with four or more ACEs at greatly increased risk of poor health status, obesity, and asthma (3.0-, 3.9-, 3.2-fold increased risk, respectively, relative to those with zero ACEs).[420,504] The intergenerational transmission of ACE-Associated Health Conditions (AAHCs) such as obesity and diabetes can also occur when parental ACEs lead to increased health risk in the parent, and then this health risk is passed directly to their offspring. For example, children with obese parents were 2.2-fold more likely to be obese themselves.[505] Likewise, maternal gestational diabetes (2.5-fold) or parental diabetes outside of pregnancy (5.8-fold and 2.7-fold increased risk for mother and father, respectively) both increased risk for the child having diabetes.[506,507]

Immune system dysregulation

Chronic stress and adverse experiences are associated with inflammation.[508,509] Inflammation is a mechanism through which chronic stress is biologically embedded and may be passed on to the next generation.[12,510] Prenatal stress exposure has been linked to increased markers of inflammation, including NF-κB, AP-1, IL-6, IL-8, and CRP.[511,512] Using asthma as an example, three systematic reviews have found a link between maternal stress during pregnancy and an increased risk for asthma in their offspring.[513-515]

Similarly, the immune status of the mother may impact the ability of the placenta to regulate the amount of cortisol that is transferred between mother and fetus. For example, inflammatory markers have been shown to alter enzymes in the placenta that regulate fetal cortisol exposure.[452] Thus, stress-mediated maternal immune status may impact fetal cortisol exposure, and thus alter fetal brain development and fetal HPA axis function throughout life.[452]

Microbiome

Within our intestines live trillions of bacteria that help us break down our food,

support our immune system, and may impact our nervous system as well.[516] In a study of 48 healthy pregnant women, a high ACE score was associated with an altered maternal gut microbiome.[517] The composition of a mother's vaginal, breastmilk, and skin microbiome during pregnancy, birth, and rearing may alter the baby's prenatal and postnatal growth, as well as brain and immune system development.[518,519]

CAREGIVER BEHAVIOR

ACEs are associated with increased risky behaviors, including smoking, alcohol dependence, substance dependence, interpersonal violence, and self-directed violence.[2,21,34,35,520-524] While these behaviors may be coping strategies adaptive to the stressful environment, they can also involve biological survival pathways, such as unconscious habits and cravings associated with changes to the mesocorticolimbic system, or reward circuit of the brain—in particular, the ventral tegmental area and nucleus accumbens.[525-527] These behaviors can themselves be ACEs for the children of those who exhibit them. ACE-related behaviors can also increase the risk for ACEs in the next generation through social learning (in which children model the behavior of their caregivers), attachment disruption, and associated parenting styles.

Risky caregiver behaviors may be ACEs for their children. ACEs are associated with increased risk of mental, behavioral health, and social conditions, such as depression, substance dependence, suicidality, intimate partner violence, and incarceration. Maternal ACEs have been associated with increased risks in the perinatal period, such as for maternal depression,[428,528-530] smoking and illicit drug use,[531] self-harm ideation,[532] teen pregnancy,[447] post-partum psychiatric episodes or illness,[533] PTSD,[529,534] and increased weight,[504] all of which can lead to ACEs for their children. Similarly, in a study of fathers, paternal ACEs were associated with paternal anxiety and depression.[535] These conditions among parents can then become ACE exposures for their children.[2,422] In addition, there is evidence that parents' behaviors are risk factors for the same behaviors in their offspring. Anda and colleagues found that children growing up with alcoholic parents were more likely to have additional ACEs, and that increasing ACE scores were associated with increased depression and alcohol dependence in adulthood, regardless of parental alcohol abuse history.[536] Unfortunately, this study was not able to clarify the role of genetic versus environmental transmission of risk.

Further, a meta-analysis of the intergenerational transmission of child maltreatment that included 84 studies found that offspring of parents who experienced maltreatment are at an almost three-fold increased risk for perpetrating child maltreatment themselves (versus having parents who did not experience child

maltreatment).[537] However, the authors point out that study quality varied and the effect was smallest for physical abuse. There is a common perception that "hurt people hurt people," but it may be more appropriate to say that "people who hurt are more likely to have been hurt themselves." According to Dr. James Garbarino, a psychologist and advocate for juvenile offenders, "Approximately only 0.01% of Americans (1 in 1000) report an ACEs score of 8, 9, or 10. The scores reported by the last 10 killers I interviewed had an average score of 8."[538] The distinction is important because ACEs are much more common than the perpetration of child maltreatment. Thus, while an ACE score is not a valid predictor of violence perpetration, early detection of ACEs and treatment of toxic stress may represent a meaningful violence prevention strategy.

Additionally, not all perpetrators have a reported history of abuse, suggesting that ACEs are one pathway to increased risk for violence, but not the only one.[539] Thus, it is important not to use an ACE score to stigmatize or prematurely punish survivors as perpetration involves a complex set of factors.

Social learning

While social learning has been found in some studies to be a possible mechanism linking parental behavior and future behavior of their offspring, the data are limited and mixed. A number of studies have found IPV to be associated with social learning as a mechanism for transmission from one generation to the next.[540] However, studies suggest other mechanisms listed below are equally if not more relevant.

Parenting style

Traumatic childhood experiences may affect parental behavior and parenting, leading to an increased risk of offspring exposure to ACEs.[417,499] An inept, coercive parenting style has been associated with antisocial behavior in children, and this, in turn, has been associated with future risk for IPV.[540] Similarly, parenting without clear rules, monitoring, or positive involvement was associated with future adolescent substance use.[541]

Attachment disruption

ACEs may alter parenting behavior and attachment, leading to a higher likelihood of detached parenting, neglect, or other negative parenting traits that are risk factors for a child's future mental health.[409,542,543] Numerous studies have shown the importance of caregivers and secure attachment for children's development.[102,306,544-550] For example, research by Bowlby showed that infant monkeys needed affection to mature into healthy, well-adjusted adults.[549] Meaney found that infant rats who were raised by highly nurturant caregivers (biological or foster)

had improved stress biology.[306,551] Diamond identified the importance of an enriched environment, including the impact of relational health on brain growth.[544,545] Lieberman and colleagues described how caregivers can be angels in the nursery, highlighting a strengths-based approach to interventions, including Child-Parent Psychotherapy.[550,552] Insecure or fearful attachment may lead to decreased trust, increased fear of abandonment, and affective instability.[540]

Importantly, social support appears to be a main pathway in mitigating the risk for transmission of behavior. Safe, stable, and nurturing relationships can break the intergenerational cycle of abuse.[544] Positive parent–child interactions have been shown to improve resilience later in life.[553] Parent engagement mitigated risk for adolescent smoking even when the parent themselves smoked.[554] Positive childhood experiences (PCEs), such as being able to talk to family about feelings, participating in community traditions, and feeling supported by friends, have been associated with decreased depression, better mental health, and improved social and emotional support in adulthood.[41] This is further evidence that PCEs and the promotion of safe, stable, and nurturing relationships can break the intergenerational cycle of adversity.[41,544]

SOCIETAL INFLUENCES

Increased ACEs are associated with an increased risk for challenging social determinants of health (SDOH) conditions.[38] Structural inequities, including lack of community investment, educational resources, economic opportunities, and transportation availability, all affect development, health, and quality of care.[555] Both interpersonal and structural racism also promote toxic stress.[556,557] Such factors significantly contribute to the perpetuation of ACEs and toxic stress across generations. For example, there is a dose–response relationship between ACEs and housing insecurity and homelessness, which, in turn, are considered risk factors for toxic stress themselves.[558,559]

The association of worse maternal health outcomes in Black and Native American women than in other demographic groups is thought to be due, in part, to pre-pregnancy stress, trauma, discrimination, and other challenging SDOH.[436,560,561] Poverty and discrimination as a result of historic and structural racism have been demonstrated to adversely affect both the diurnal rhythms and feedback loops of the stress response system, as well as the interface between the HPA axis and other systems critical for maintaining health, such as immune functioning.[436,460,510,562,563] Keenan and colleagues postulated that a primary cause of disparities in maternal and child health among Black Americans is likely due to a disproportionate amount of stress experienced by this group.[436] As noted above, stress experienced not only by the individual, but also by past generations, can impact health status through

epigenetic and other mechanisms. Policies, systems, and societal norms must address historical and current racial trauma as well as implement strategies to decrease the burden of toxic stress for minorities and marginalized communities.

Factors considered SDOH can exacerbate intergenerationally transmitted biological and behavioral risks, but are not generally considered to be transmitted themselves, due to their external nature. An effective public health and policy response to ACEs and toxic stress must include strategies to address the SDOH that perpetuate cycles of trauma, poor health, and negative social outcomes (see **Part II**).[564]

Historical and cultural trauma

The impacts of an individual's early exposure to adversity and stress may be passed through several generations. Recent scientific advances have begun to uncover the mechanisms of this longer-range intergenerational transmission.[303,414,565,566] Studies, reviews, and commentaries have evaluated the offspring of survivors of the Holocaust,[476,565,567] Native American genocides,[568-571] 9/11,[572,573] and slavery.[574-576]

These studies highlight the intergenerational transmission of adversity through direct biological mechanisms, including those discussed in this report, as well as political, economic, environmental, and social/ecological pathways, rather than simply through effects of the parent's emotional state and behaviors.[577] These studies also provide a valuable frame to expand from a focus solely on the transmission of ACEs from an individual to their offspring to that of historical trauma passed from one generation to the next. Bringing the lens of historical trauma to trauma work "creates an emotional and psychological release from blame and guilt about health status, empowers individuals and communities to address the root causes of poor health, and allows for capacity-building unique to culture, community, and social structure."[577] Recognizing that current and historical trauma—including the murder and enslavement of Black and Native Americans—can leave biological imprints on the health of current and subsequent generations, adding to the moral imperative and obligation to heal these harms.

CONCLUSION

ACEs and other early life stressors cause a chicken-egg cycle of intergenerational risk for toxic stress and poor health outcomes. However, emerging science is illuminating what was formerly the black box of toxic stress, highlighting mechanisms between ACEs, toxic stress, and health. In this way, science offers new opportunities to more precisely interrupt the intergenerational cycle of ACEs and toxic stress, and to promote an intergenerational cycle of health. The skills children need to be resilient and healthy can all be learned from attuned, engaged,

and nurturing adults. Evidence suggests that early intervention can improve brain, immune, and genetic regulatory control of development and is therefore critical for improving outcomes for individuals at risk for toxic stress.[579-585] Treatment of toxic stress in adults may serve to prevent transmission of neuro-endocrine-immune-metabolic and genetic regulatory disruptions in offspring. This section highlights the importance of a multigenerational and multidisciplinary approach that promotes caregiver healing, family resilience, and safe, stable, and nurturing relationships to break the cycle. Curbing the intergenerational transmission of ACEs and toxic stress requires a public health approach utilizing a coordinated, multisector strategy to advance prevention, early detection, and interventions (see **Part II**).

RECOMMENDATIONS

Prevention

1. Raise national awareness through communication, policy, and action efforts, that ACEs and toxic stress can be passed down from generation to generation—but so can protective factors.
2. Community and ecological action: collaborate across child-serving sectors to create accountable communities and collective, equitable action.
    - **a.** Highlight transmission of protection and resilience.
    - **b.** Interventions at any point are primary prevention for the next generation.
    - **c.** Patience and perseverance: recognize that if it takes time to cause dysregulation, it can take time to reverse it.
    - **d.** Biologically based approaches to policy, advocacy, and interventions, including trauma-informed care, strength-based approaches, and attention research-based stress-mitigation strategies; if ACEs and toxic stress can increase risk for poor health in one generation, promoting relational health will decrease ACEs and toxic stress in the next.
    - **e.** Focus on reducing racism and bias everywhere, including in the delivery of healthcare, as a key highlighted goal for primary prevention.
3. Family and multi-generational approach.
    - **a.** Supporting caregivers in treating impacts from their own ACEs.
    - **b.** Family-focused therapies, such as Child-Parent Psychotherapy,[586,587] are two-generation treatment approaches which address ACEs for both caregiver and child. (See **Tertiary Prevention Strategies in Healthcare**

in Part II for further description of these and other evidence-based therapies.)

Practice transformation

1. Universal screening: ensuring universal screening for cumulative adversity and risk of toxic stress in the preconception, prenatal, and postnatal periods.
2. Promote relational health and safe, stable, and nurturing relationships, which are known to mitigate effects of parental adversity, both during childhood and into adulthood.
    a. Support programs such as Centering Parenting[588] and the CDC's Legacy for Children,[589] which provide the proactive social supports to promote positive parenting and positive child health outcomes, rather than waiting for the child's ACE score to rise.
    b. Implement sufficient social supports for young parents and families.
3. Effective referral systems: strengthening referral systems to help children, adults, and families access appropriately targeted services can interrupt or mitigate toxic stress physiology.
4. Comprehensive service array: comprehensive services to address ACEs, toxic stress, and accompanying SDOH that can be coordinated through a primary care home (especially in rural and underserved communities) for both children and adults, can interrupt the intergenerational transmission of ACEs.
5. Payment for services.
    a. Secure public (e.g. Medicaid) and private insurer payment for routine screening and treatment for toxic stress in every state.
    b. Explore payment reform such that preventative interdisciplinary primary care is reimbursed at rates comparable to those paid for disease care and procedural services.

Research and innovation

1. Advance the science to measure, mitigate, and treat the effects of ACEs and toxic stress in children and adults. Enhance understanding of clinically viable biomarkers for diagnosing and monitoring toxic stress, as well as biologically precise therapeutic targets for treatment of toxic stress. In research, identify consistent measures of toxic stress to be able to compare across studies.
2. Increase research on interventions that heal toxic stress and improve

health.

   a. Evaluate impacts of interventions on neuro-endocrine-immune-metabolic and genetic regulatory disruption, health outcomes, and measures of health.
   b. Increase focus on researching which interventions work best in what circumstances, for which populations, and for which health conditions.

3. Promote a strengths-based research framework that studies how to proactively build relational health that not only buffers adversity when it occurs, but also promotes the social-emotional and cognitive skills to be resilient in the future.
4. Utilize machine learning and big-data computational analyses to identify how timing, severity, and predisposing factors contribute to differences in generational patterns of health outcomes. More precisely evaluate effects of exposure timing, moderating impacts, and the cumulative effects of adversity and resilience factors.

Of note, all recommendations made are subject to the budget approval process.