

Tertiary Prevention Strategies in Healthcare

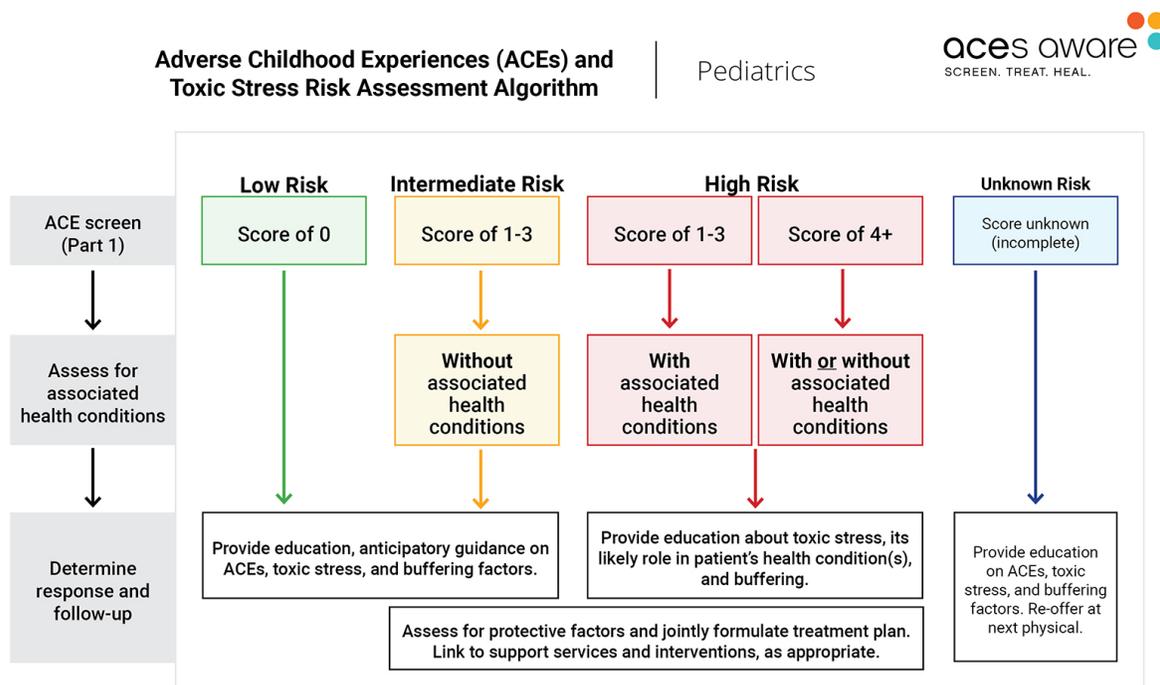
This section's goal is to offer strategies and interventions to reduce the impact of the toxic stress response, once these physiological processes are already underway. There is an urgent need for healthcare providers to be familiar with the toxic stress response, the ways in which it can alter physiology, and evidence-based or promising practices for treatment. While the American Heart Association and other entities have increasingly recognized Adverse Childhood Experiences (ACEs) as a significant risk factor for chronic disease,⁷⁴⁹ few, if any, clinical treatment guidelines incorporate strategies for mitigating the toxic stress response.

This section summarizes current science and clinical practice for supporting individuals with positive ACE screens (i.e., those who are assessed to be at intermediate or high risk for toxic stress). It offers information on interventions that target the underlying biological mechanisms of toxic stress to improve neuro-endocrine-immune-metabolic functioning and ACE-Associated Health Conditions (AAHCs). Overall, the goal is to highlight tools and interventions that can be used in the primary care setting, as well as strategies for trauma-focused partnerships and referrals. Moving forward, evidence-based treatment guidelines to address the role of toxic stress physiology in the treatment of AAHCs are necessary, such as for asthma, autoimmune disease, cardiovascular disease, and mental health disorders.

DIAGNOSIS

As discussed in the previous section, ACE screening involves assessing for the triad of adversity (ACE score), clinical manifestations of toxic stress (AAHCs), and protective factors. The first two components are used in assessing clinical risk for toxic stress and all three help to guide effective responses. Of important note, there currently exist no widely agreed upon clinical diagnostic criteria for toxic stress, and the toxic stress response is not listed in the International Classification of Diseases (ICD). Although the biological mechanisms of toxic stress are well supported by a consensus of scientific evidence, further research is necessary to determine whether the toxic stress response is best characterized as a condition, a disorder, or a disease.

In the absence of clinical diagnostic criteria, the combination of ACE score and the presence or absence of AAHCs may serve as a somewhat crude, but useful, proxy for the likely presence of a toxic stress response. Pending the development of confirmatory diagnostic criteria and/or biomarkers, the evidence supports characterizing a patient as being at low, intermediate or high risk of manifesting a toxic stress response. The ACEs and Toxic Stress Risk Assessment Algorithms (Figures 8 a,b) for pediatric and adult care were created by a team of expert researchers and clinicians, led by the Office of the California Surgeon General, to assist providers who screen for ACEs in assessing risk for toxic stress.⁸⁶



This algorithm pertains to the ACE score (Part 1 of PEARLS), whose associations with health conditions are most precisely known. Social determinants of health (Part 2 of PEARLS) may also increase risk for a toxic stress response and should be addressed with appropriate services, but should NOT be added to the ACE score for this algorithm. Partial completion may indicate discomfort or lack of understanding. If partial response indicates patient is at intermediate or high risk, follow the guidelines for that category.

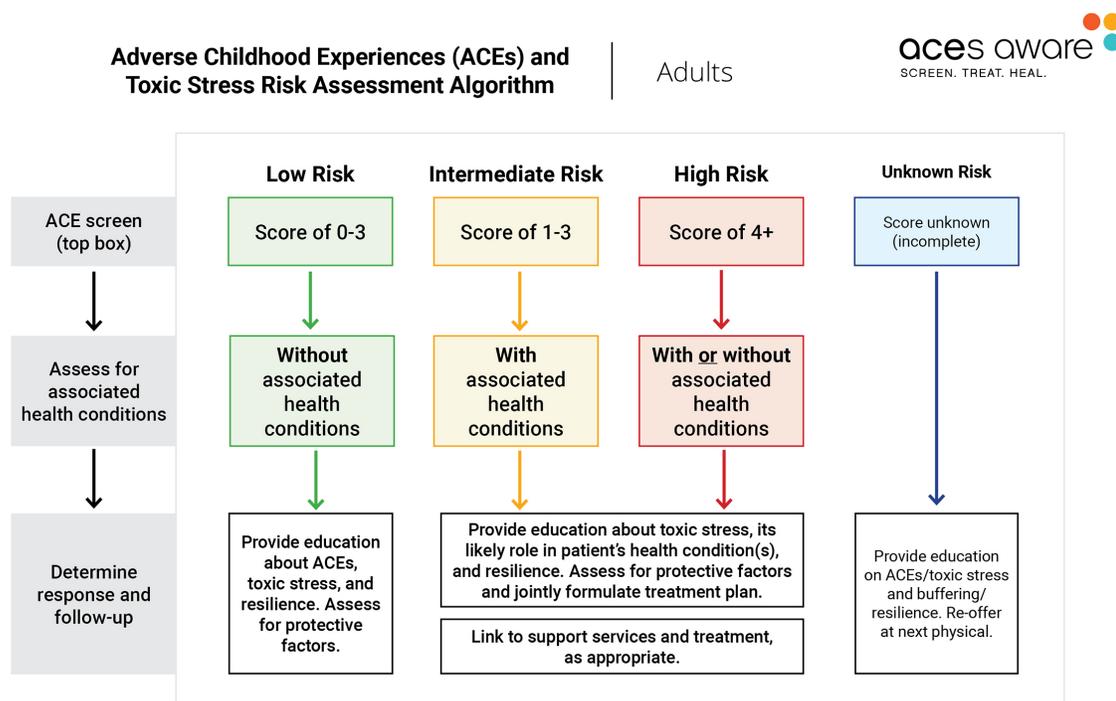
If the ACE score is 0, the patient is at "low risk" for toxic stress. The provider should offer education on the impact of ACEs and other adversities on health and development as well as on buffering factors and interventions. If the ACE score is 1-3 without ACE-Associated Health Conditions, the patient is at "intermediate risk" for toxic stress. If the ACE score is 1-3 and the patient has at least one ACE-associated condition, or if the ACE score is 4 or higher, the patient is at "high risk" for toxic stress. In both cases, the provider should offer education on how ACEs may lead to toxic stress and associated health conditions, as well as practices and interventions demonstrated to buffer the toxic stress response, such as sleep, exercise, nutrition, mindfulness, mental health, and healthy relationships. The provider should also assess for protective factors, jointly formulate a treatment plan, and link to supportive services and interventions, as appropriate.

Figure 8a. ACEs and toxic stress risk assessment algorithm for pediatrics. Reproduced with permission from ACEs Aware.⁸⁶

CLINICAL RESPONSE

Anticipatory guidance, interventions, and referrals should start with addressing any immediate safety concerns, and attention to the key principles of trauma-informed care (TIC), reviewed in the last section (**Primary and Secondary Prevention Strategies in Healthcare**).

This section on tertiary prevention offers research-based tools that are associated with mitigation of toxic stress. The strategies that follow can also be used as a framework for a meaningful and supportive approach that emphasizes strengths and intervention options for managing toxic stress. For example, an adult patient found to be at low risk of toxic stress (ACE score of 3, no associated symptoms or



Partial completion may indicate discomfort or lack of understanding. If partial response indicates patient is at intermediate or high risk, follow the guidelines for that category.

If the ACE score is 0-3 without ACE-Associated Health Conditions, the patient is at "low risk" for toxic stress physiology. The provider should offer education on the impact of ACEs and other adversities on health (including reviewing patient's self-assessment of ACEs' impact on health), buffering/protective factors, and interventions that can mitigate health risks. If the ACE score is 1-3 with ACE-Associated Health Conditions, the patient is at "intermediate risk." If the ACE score is 4 or higher, even without ACE-Associated Health Conditions, the patient is at "high risk" for toxic stress physiology. In both cases, the provider should offer education on how ACEs may lead to a toxic stress response and associated health conditions, as well as practices and interventions demonstrated to buffer the toxic stress response, such as sleep, exercise, nutrition, mindfulness, mental health, and healthy relationships. The provider should also assess for protective factors, jointly formulate a treatment plan and link to supportive services and interventions, as appropriate.

Figure 8b. ACEs and toxic stress risk assessment algorithm for adults. Reproduced with permission from ACEs Aware.⁸⁶



Figure 9. Employing the evidence-based strategies for toxic stress regulation can help patients reduce stress and build resilience. Reproduced with permission from ACEs Aware.²⁶

conditions) and with a number of protective factors may not need any additional interventions or referrals beyond patient education. However, a patient determined to be at intermediate risk of toxic stress (ACE score of 1, with symptoms of depression and poorly controlled asthma) and with limited social supports may benefit from specific interventions that target the toxic stress response, as well as referrals for community and/or mental health resources.

The stress-mitigation strategies listed below can be used as a framework for patient education and as an adjunct to usual care for AAHCs, as they have all been shown to reduce stress hormones, reduce inflammation, and enhance neuroplasticity^{603,750-759}—key mechanisms to counteract the toxic stress response and improve overall health and well-being. These strategies offer an integrative approach to ACEs and toxic stress intervention:

- Healthy relationships
- High-quality, sufficient sleep
- Balanced nutrition
- Regular physical activity
- Mindfulness and meditation
- Access to nature
- Behavioral and mental healthcare

HEALTHY RELATIONSHIPS

Relational health is a relatively new term used to highlight the growing body of science detailing the importance of relationships to health and well-being.^{102,544-546,549,551,760,761} Research shows that relationships can buffer stress and reduce, or in some cases, eliminate the negative health impacts associated with ACEs.^{604,762}

HPA axis and cortisol

A growing body of research is identifying the positive impacts of relational health on neuro-endocrine-immune-metabolic function. In rats and primates, nurturing maternal interactions inhibits hypothalamic-pituitary-adrenal (HPA) axis reactivity in the presence of stressors.^{750,763} Responsive caregiving mediates improved cortisol reactivity in children, and is associated with reduced health impacts of ACEs.^{750,751}

Cardiovascular reactivity and autonomic nervous system

Social support is associated with lower blood pressure and a decreased risk for cardiovascular disease.⁷⁶⁴ Supportive relationships have been shown to buffer stress-induced cardiovascular reactivity and are associated with lower plasma and urinary catecholamine (stress hormone) levels.⁷⁶⁵

Immune function

Social support and Positive Childhood Experiences (PCEs) have also been associated with decreased asthma symptoms and improved immune responses, including inhibiting inflammation, providing protection against infection, and promoting wound healing.⁶⁶⁸⁻⁶⁷² Social support can predict natural killer cell activity and helper T cells in HIV-positive individuals,⁷⁶⁴ and has also been linked to decreased susceptibility to common cold.⁷⁶⁴ Greater social integration has shown a dose-dependent association with reduced susceptibility to clinical illness and viral-specific antibody levels across two viruses.⁷⁶² Another study by the same group found that hugging had a stress-buffering, immune-protective effect and explained 32% of the attenuating effect of support on infection risk.⁷⁶⁶ Relational health has also been associated with decreased markers of inflammation.⁷⁶⁴

Oxytocin

One mechanism by which supportive relationships are believed to lead to health-protective effects is through release of the hormone oxytocin. Oxytocin is produced in the hypothalamus and enhances bonding, inhibits the stress response, protects against stress-induced cell death, has anti-inflammatory effects, enhances metabolic homeostasis, and protects vascular endothelium.^{671,672,767-769} It is released in high quantities during childbirth and lactation and is most widely used clinically for augmentation of labor.^{767,770}

The amygdala (the brain's threat detector) has oxytocin receptors, allowing oxytocin to inhibit the amygdala-induced stress response, thereby inhibiting both the sympatho-adreno-medullary (SAM) and HPA axes, which constitute the fight-flight-or-freeze pathways.⁷⁶⁷ Oxytocin has been associated with reductions in anxiety and stress, and can modulate trust and social memory.⁷⁶⁷ Oxytocin has been suggested to inhibit stress-hormone-related neuronal cell death in the hippocampus, a brain structure involved in memory.⁷⁶⁸ Oxytocin also appears to be involved in safety learning and extinguishing fear when safe⁷⁷¹ and has been shown to support interoceptive (internal awareness) sensitivity and lower somatic problems in children.⁷⁷² The tend-and-befriend response to stress, possibly more prominent in females, may also be linked to oxytocin release.^{773,774}

Oxytocin has been investigated as a potential therapeutic agent for several AAHCs. Research to date is mixed, but suggests that oxytocin may support cardiovascular health, including reversing atherosclerosis associated with heart disease,⁷⁶⁹ promoting weight loss, metabolism of sugar and fat, insulin sensitivity,⁷⁷⁵ mitigating post-traumatic stress disorder (PTSD), antisocial symptomatology,⁷⁷⁶⁻⁷⁷⁹ strengthening immune defense, inhibiting inflammation, and promoting wound healing.^{671,672}

However, oxytocin is also associated with increased self-versus-other distinction,⁷⁸⁰ which can increase us-versus-them thinking and lead to greater sensitivity to social threats.^{780,781} Increases in hostility, aggression, and parasympathetic response to interpersonal threat have also been associated with oxytocin.^{780,782} Further research on potential therapeutic uses of oxytocin to mitigate toxic stress is warranted.

Assessment of relational health

While there are a number of validated, research-based tools to evaluate attachment and relational health, there are very few short, dynamic screens available for easy use in primary care clinical practice. While tools such as the Protective Factors Survey may be useful, providers are also encouraged to have an open conversation with their patients about relational health and specifically ask about perceived social support (Do you feel you have someone who understands and believes in you, who you could talk to when you are upset?), received social support (When needed, do you have someone that can give you emotional, financial, or material support—for example, a car ride to the clinic?) and social integration (Do you feel you belong and are part of a group/community?). If relational health issues are identified, the strategies and programs presented below can support healthy relationships and connections within the community. Referrals to these needed resources can be included with other referrals.

Relational health in pediatrics

There are a number of programs that have been developed to support the child-caregiver relationship that can be used in the pediatric primary care clinic setting.^{783,784} Universal primary prevention, including routine anticipatory guidance about relational health and developmentally appropriate play such as Talk. Read. Sing.⁷⁸⁵ and clinic programs such as Reach Out and Read,^{786,787} have been recommended by the American Academy of Pediatrics. Key components of high-quality programs include opportunities for parents and patients to network with and receive support from peers who have been in similar situations, engaging fathers, and treating parents and patients as equal partners.^{553,788}

Of note, the intergenerational pattern observed with ACE transmission reflects that children with high ACEs often have parents with high ACEs. Some dyadic or two-generation interventions specifically target addressing parental trauma as a means to improve child outcomes. Targeted interventions to repair strained relationships include Attachment and Biobehavioral Catch-up (ABC), Child-Parent Psychotherapy (CPP), and Parent-Child Interaction Therapy (PCIT).^{699,789-791}

These interventions have been associated with improvement in various markers of neuro-endocrine-immune-metabolic regulation, including cortisol, epigenetic regulation, and brain development.^{603,792,793} ABC has been found to improve child attachment, cortisol levels, emotion regulation, executive functioning, as well as increased parent sensitivity to their child.⁷⁸⁹ CPP has been associated with improvements in child behavioral problems and child traumatic stress disorder symptoms,⁵⁸⁷ as well as protecting against telomere shortening.⁴⁹² PCIT has been shown to decrease negative parent-child interactions,⁷⁹¹ and to reduce child aggressive behavior and cortisol levels.⁷⁹²

A systematic review of interventions in pediatric care to improve ACE-related child outcomes found that multicomponent interventions including parenting education, mental health support, and social service referrals were associated with improvements in parent-child relationship and behavioral and mental health problems.⁷⁹⁴

Adolescents and adults

Difficult relationships during childhood may affect the ability to make meaningful and trusting personal connections or engage in group activities. If indicated, referral for individualized mental health therapy may help patients overcome issues with trust and safety, and develop skills to form healthy relationships. (See the subsection on Mental and Behavioral Health below.)

Providing education about healthy relationships can help patients and caregivers

understand the normal and expected reactions to ACEs and toxic stress so that they can better regulate themselves and respond to others in challenging situations. The patient-provider relationship can be a model for the healthy relationships providers hope to promote for their patients. This includes supporting self-care for healthcare providers to reduce burnout and compassion fatigue.

KEY TAKEAWAYS: HEALTHY RELATIONSHIPS

- > Key aspects of relational health include having safe, stable, and nurturing relationships and environments.
- > Relational health has been associated with improved mental, cognitive, cardiovascular, and immune health, and has been shown to buffer the stress response system.
- > Difficult relationships during childhood may affect the ability to make meaningful and trusting personal connections or engage in group activities.
- > Patients and clients may be encouraged to connect with supportive relatives, friends and community activities.
- > Improving relational health requires an individual, family and community approach.
- > The patient-provider relationship can be a model for the healthy relationships providers hope to promote for their patients.
- > Self-care for health providers is an essential component of trauma-informed clinical care.

SLEEP

Sleep disturbances are among the most common and nonspecific outcomes of childhood adversity.^{795,796} Stress can cause increased, decreased, or disordered sleep,⁷⁹⁵⁻⁷⁹⁷ and children and adults with a history of ACEs may be more vulnerable to the effects of subsequent stressors due to sensitization of the stress response.⁷⁹⁸⁻⁸⁰⁰

A systematic review of ACEs and sleep disorders found associations between family conflict in childhood and insomnia at 18 years of age, as well as between child sexual abuse and sleep disturbances.⁷⁹⁶ Nightmares are one of the intrusion symptoms involved in PTSD diagnosis; however, additional disruptions in sleep have also been noted. Researchers are currently investigating the development of criteria for “trauma-associated sleep disorder” (TASD), which would include nightmares, disruptive nocturnal behaviors (moaning, screaming, tossing, turning, or thrashing), increased heart rate, more rapid breathing, and sweating.⁷⁹⁷

Poor sleep is linked with poor health outcomes. Disordered or reduced sleep duration is associated with heart disease, hypertension, obesity, diabetes, cancer, decreased cognitive performance, depression, anxiety, inflammatory diseases, infection risk, and all-cause mortality.^{752,753,801-804} In children, poor sleep is associated

with impairments in neurocognitive development, social emotional skills, physical health, and family functioning.⁸⁰⁵ Understanding the mechanistic pathways linking trauma, disordered sleep, and poor health outcomes can help direct interventions.

Neuroendocrine pathways

Normal sleep increases growth hormone, prolactin, and melatonin, and supports memory consolidation.^{752,753,802,804} Healthy sleep also allows for the normal circadian rhythms of cortisol levels and supports decreases in sympathetic nervous system (SNS) output.^{752,753} Adversity and toxic stress may impair sleep by dysregulating cortisol and SNS activity.^{752,753,806} The reverse has also been found: profound sleep loss can activate the fight-flight-or-freeze system.⁷⁵² Disruptions in sleep are associated with altered levels of cortisol,⁸⁰⁴ as well as increases in norepinephrine, epinephrine, and blood pressure.⁷⁵²

Poor sleep alters other endocrine and metabolic functions. Sleep deprivation can increase appetite and caloric intake.⁸⁰⁴ It is also associated with elevated insulin and blood glucose levels and altered brain glycogen.⁸⁰⁴ In adolescents, short sleep has been independently associated with insulin resistance.⁸⁰⁷

Immune pathways

Sleep deficiency disturbs immune system homeostasis and is associated with chronic, low-grade inflammation.^{752,802} Healthy sleep is associated with a reduced risk of infection, improved infection outcomes, and improved response to vaccination.⁸⁰² It is associated with early increases in inflammatory markers needed for healthy immune function, while later in sleep, counterregulatory processes develop.⁷⁵² Natural killer cell activity increases over the course of sleep, as do inflammatory markers IL-6 and TNF, which can affect immune response.⁷⁵² Unhealthy alterations in sleep are associated with altered immune cell counts and dysregulation of these inflammatory markers.⁷⁵²

It is important to note that immune activation may also disrupt sleep.⁸⁰² In animal studies, IL-1, TNF, and PGD2 promoted non-REM sleep and at high doses, may suppress REM sleep.⁸⁰² Research is still exploring how these domains of stress regulation are interrelated.

Assessment of sleep

While there are validated sleep-assessment tools, such as the Pittsburgh Sleep Quality Index and the Insomnia Severity Index, the most pragmatic approach for a busy clinic may be to highlight four key elements: patient satisfaction with sleep, whether patients feel restored and rested when they wake up, whether they have trouble falling asleep initially, and whether they have trouble staying asleep or

falling back to sleep if they wake up in the middle of the night.⁷⁵² Sleep diaries, sleep apps, actigraphy (wearable devices), and polysomnography can be used when more data is needed, especially if there is concern for obstructive sleep apnea or sleep-disordered breathing.⁷⁵²

Behavioral strategies

Interventions to support healthy sleep can decrease stress and improve health outcomes. Generally, behavioral techniques and education about healthy sleep habits (also known as sleep hygiene) are first-line interventions.^{808,809} These include eliminating electronics, caffeine, alcohol, and exercise close to bedtime; creating a sleep routine; using the bed for sleep (and, for adults, sex) only; and getting out of bed if one cannot sleep.⁸¹⁰ A meta-analysis of sleep interventions for adults without diagnosed sleep disorders found that cognitive and behavioral interventions, including relaxation practices, sleep hygiene, and exercise improved sleep quality.⁸¹¹ In addition, the triad of healthy nutrition, exercise during the day, and sleep has been shown to reduce the risk of developing neuropsychiatric disorders.⁸¹²

A consistent bedtime routine improves sleep, child mood, emotional behavioral regulation, mother's self-reported mood, school readiness, and literacy outcomes (especially when reading is part of the bedtime routine); it has been associated with decreased bedtime tantrums (and associated improvements in marital satisfaction) and can be a buffer against parenting stress.^{805,813,814} Bedtime routines can create a sense of predictability and stability known to support trauma healing and resilience building.⁸¹⁵ Bedtime routines can include feeding (for infants and children), bath, massage, reading books, rocking, prayer, singing, and listening to music.

It is important to note that children with neurodevelopmental, mental health, or trauma-related conditions may need different or more flexible bedtime routines than neurotypical children.⁸¹³ For example, children and adults experiencing nightmares, anxiety, depression, or fear may need specific coping strategies such as a night light, a weighted blanket, and relaxation techniques. Efforts to have a traumatized child sleep-train or "cry it out" may increase fear, isolation, and trauma reactions. Medical providers can remind parents about their ability to buffer the threat-response system and encourage them to discuss fears and solutions openly with their child.⁷⁰⁴

Behavioral therapies

- Parent-child groups, parenting classes, and case management in infancy and early childhood are associated with improved sleep schedules at age three years.⁸¹⁶

- Meditation, tai chi, yoga, and exercise have been shown to improve sleep quality.^{752,817-819}
- Cognitive-behavioral therapy (CBT) has been associated with reduced insomnia and decreased markers of inflammation.⁷⁵² In addition, there is a specific CBT protocol for insomnia, CBT-I.⁸¹⁰
- Imagery rehearsal therapy and exposure, relaxation, and rescripting therapy, both of which involve rescripting and rehearsing changes to a recurrent nightmare, have been shown to decrease recurrent nightmares.^{820,821}
- Medications such as melatonin or prazosin may be indicated in some cases.⁸²¹⁻⁸²⁷ Physicians and patients can together determine whether medication is an appropriate option.
- Given that inflammation can aggravate healthy sleep, studies are currently being done to evaluate the effectiveness of immune therapies for sleep. For example, TNF- α blockers have been shown to improve sleep.⁸²⁸

KEY TAKEAWAYS: SLEEP

- > Sleep disturbances in childhood and adulthood are common outcomes of childhood adversity.
- > Poor sleep is associated with increased risk for heart disease, obesity, diabetes, cancer, decreased cognitive performance, depression, anxiety, inflammatory diseases, infection risk, and all-cause mortality.
- > Healthy sleep can improve neurological, endocrine, metabolic and immune regulation and is associated with improved health outcomes.
- > Healthy sleep habits include eliminating electronics, caffeine, alcohol, and exercise close to bedtime, creating a sleep routine, using the bed for sleep (and, for adults, sex) only, and getting out of bed if one cannot sleep.
- > Children with neurodevelopmental, mental health, or trauma-related conditions may need different or more flexible bedtime routines than neurotypical children, including a night light, a weighted blanket, relaxation techniques, or conversations with a trusted adult about strategies to address specific worries.
- > Meditation, yoga, and exercise during the day can also improve sleep.
- > For people with significant sleep disturbances additional assessment and interventions may be indicated, including medications and cognitive-behavioral therapies.

NUTRITION

ACEs have been linked to increased risk of obesity, insulin resistance, and diabetes, as well as eating disorders such as anorexia nervosa and bulimia.⁸²⁹⁻⁸³² In one

study of girls, child sexual abuse was associated with increased risk of obesity (odds ratio, OR: 2.6; 95% confidence interval, CI: 1.1-6.4) and extreme weight-loss behaviors (OR: 2.2; 95% CI: 1.0-4.7), and parental unemployment was associated with obesity (OR: 3.5; 95% CI: 1.2-9.6) and being underweight (OR: 3.6; 95% CI: 1.1-11.6).⁸³⁰ In another study, a dose-response effect was noted between child trauma subtypes and the severity of eating disorder symptoms.⁸³¹ Among people with eating disorders, several systematic reviews found a higher prevalence of ACEs.⁸³³⁻⁸³⁶

Bidirectional relationship

There is a bidirectional relationship between nutrition and stress: malnutrition/undernutrition can activate the physiologic stress response, and, conversely, stress can affect food behavior, digestive processes, and metabolism.⁸³⁷ Calorie restriction has been associated with increased cortisol levels and reduced white blood cells (lymphocytes), or lymphopenia.⁸³⁸ Interestingly, alleviation of the stress rapidly reverses the lymphopenia.⁸³⁸ Maladaptive nutritional coping strategies, including preference for high-fat and high-sugar foods, can lead to increased inflammation or infection risk.⁸³⁷ Patients with eating disorders have been found to have either greater basal cortisol levels or greater cortisol reactivity.⁸³⁸ Additionally, obesity is associated with physiological stress, chronic inflammation, and oxidative stress.⁸³⁸ As an example of the interrelated pathways between food and stress, one study found food insecurity was linked to maternal perceived stress and increased fat intake, while pre-pregnancy body mass index (BMI) was associated with food insecurity status.⁸³⁹

Stress affects food behavior

Norepinephrine and epinephrine are released as part of the threat response and affect metabolic functions, including increasing glucose mobilization, insulin resistance, and glucagon secretion and decreasing gut motility and gastric emptying.^{74,839,840} Glucagon, in turn, decreases appetite.⁷⁴ Glucocorticoids, however, have been shown to stimulate appetite, especially for carbohydrates and fat.^{74,837,841} High-fat and high-sugar diets can temporarily decrease the cortisol response and feelings of anxiety and stress,^{837,839} potentially reinforcing this pattern of eating as a way to calm an overactive threat response system, and promoting risk for diabetes, cardiovascular disease, obesity, and other diet-related health effects.

Researchers have identified different time courses for the impacts of neurotransmitters; norepinephrine and epinephrine act in seconds to minutes, while glucocorticoids act in hours to days.⁷⁴ Thus, it may be that decreased appetite occurs early in the stress response, and increased appetite occurs in the later phase. Researchers suggest that many of the glucocorticoids' actions are to help

prepare the individual for future threats and that the effects of glucocorticoids on appetite and metabolism may support future stress reactions.^{74,842} Thus, under- and overeating may both be neurobiological adaptations to stress.

Neuroendocrine and immune impacts

Diet can directly affect the immune system.^{840,843} For example, produce with residual pesticides, fast food, and overly processed foods are pro-inflammatory.⁸⁴⁴⁻⁸⁴⁷ The Western diet (high in red and processed meat, saturated fats, and refined grains) has been associated with increased inflammatory markers compared to diets with greater fruit, vegetables, fish, and whole grains.⁸⁴⁰

The Mediterranean diet, which emphasizes olive oil, fish, whole grains, fresh fruit, and vegetables, has been associated with reduced inflammation and decreased risk for depression, cardiovascular disease, diabetes, and total mortality.⁸⁴³ Olive oil use has been associated with lower biomarkers of inflammation.⁸⁴³

Assessment

Given the complex and interconnected nature of diet, nutrition, stress, eating disorders, and obesity, measuring BMI and weight alone are not sufficient to assess nutritional status.⁸⁴⁸ Patient completion of a 24-hour food recall or a food diary (which can be supported with downloadable apps) can be useful clinical techniques.

Interventions

Given the literature identifying the strong link between stress, nutrition, and neuro-endocrine-immune-metabolic functioning, an adequate and balanced diet, as well as nutritional supplementation, may help support regulation of the toxic stress response.

It is important to consider from the outset how patient education around diet and weight is given. Nutritional counseling for patients found to be at intermediate or high risk for toxic stress should include consideration of the biological drive for high-fat, high-sugar foods and the complex interplay between food, stress, and neuro-endocrine-immune-metabolic function. Any implication that dietary choices and weight gain are due solely to lack of willpower and poor personal choices is not biologically accurate. A trauma-informed approach can help decrease blame and shame and identify a more comprehensive strategy to treat eating disorders or obesity as part of a toxic stress phenotype.

Trauma-informed strategies to support healthy eating habits include helping patients identify healthy forms of high-fat, high-energy foods, such as nuts, yogurt, fish, and avocados, and offering strategies to increase use, including

storing them in easily accessible places (while putting the junk food in hard-to-reach places or gradually eliminating it). Recognizing that toxic stress can lead to inflammation, medical providers may consider offering patient education about anti-inflammatory diets, such as those high in fruits and vegetables, and low in pro-inflammatory foods, such as fast food and overly processed foods.

Several researchers have highlighted the importance of specific nutritional interventions in decreasing stress and inflammation.^{849,850}

Polyunsaturated fats

Polyunsaturated fats support brain function, cell membrane transport, and production of neurotransmitters.⁸³⁷ Omega-3 fatty acids are in fish, walnuts, and flaxseed and have been found to block NF-kappa β , decrease TNF- α , and decrease oxidative stress.⁸⁴⁴ Diets low in omega-3 fatty acids have been associated with higher levels of anxiety and depression in pregnancy.^{851,852} Nutritional supplementation with omega-3 fatty acids has been found to lower norepinephrine, adrenocorticotrophic hormone, plasma cortisol, and body temperature in response to an endotoxin challenge, compared to a placebo.⁸⁴⁴ Two specific omega-3s, eicosapentaenoic acid and docosahexaenoic acid, have both been shown to decrease stress-related depression, anxiety, violence, and aggression.⁸³⁸

In double-blind, randomized, placebo-controlled studies, nutritional supplementation with omega-3 fatty acids for children was associated with improved child behavior and decreased aggression and intimate partner violence among parents, but did not impact child maltreatment.^{853,854} Omega-6, found in refined vegetable oils, competes with omega-3 for the same receptors and may interfere with omega-3 uptake. Omega-6 intake has been associated with increases in inflammatory markers IL-1, TNF-alpha, and IL-6.⁸⁴⁴

Breastfeeding

Breastfeeding is associated with decreased infection risk, improved cognitive development, decreased postpartum depression, and may facilitate mother-child bonding.^{805,848,850} Responsive feeding practices can improve child development even more when combined with nutritional support.⁸⁵⁰ In addition, eating meals with family and community can be a source of cultural and relational support.⁷⁰⁴

While there is much promise, further research is needed to provide specific recommendations for diet or nutritional supplementation as a way to improve neuro-endocrine-immune-metabolic function in the setting of ACEs and toxic stress.

KEY TAKEAWAYS: NUTRITION

- > ACEs and toxic stress have been associated with obesity, insulin resistance, diabetes, and eating disorders such as anorexia.
- > Stress can increase or decrease appetite.
- > Stress can increase craving for high-fat and high-sugar foods.
- > The Western diet (high in red and processed meat, saturated fats, and refined grains) has been associated with increased inflammation.
- > Diets with greater fruit, vegetables, fish, and whole grains have been associated with decreased inflammation and improved health.
- > Patients may be encouraged to consider healthy forms of high-fat, high-energy foods, such as nuts, yogurt, fish, and avocados when craving high-fat, high-sugar foods.
- > Patients should be encouraged to use habit formation strategies to increase intake of anti-inflammatory foods (fruits, nuts, vegetables) by storing them in easily accessible places (while putting the junk food in hard-to-reach places).

PHYSICAL ACTIVITY

Physical activity is known to improve health, including reducing risk of cardiovascular disease, diabetes, mental health disorders, and all-cause mortality.⁸⁵⁵⁻⁸⁵⁹ Health benefits include those potentially mediated by improvements in neuro-endocrine-immune-metabolic functioning.

Neurologic impacts

Ample research demonstrates the positive effects of physical activity on brain health. Exercise releases proteins such as brain-derived neurotrophic factor (BDNF) and metabolites such as lactate, which can cross the blood-brain barrier and may support brain health.^{754,860} A meta-analysis found that higher exercise intensity and longer durations were associated with higher acute increases of BDNF and/or changes in BDNF basal level.⁸⁶¹ BDNF is a potential link between physical activity and brain health, and is associated with neuronal growth and improved neuroplasticity.^{861,862} Interestingly, there appears to be a dose-response relationship between aerobic exercise and BDNF levels, but not between strength training and BDNF levels.⁸⁶³

Exercise training increases hippocampal perfusion and hippocampal volume, specifically the anterior, left, and right hippocampus.⁸⁶⁴⁻⁸⁶⁶ Physical activity increases hippocampal white matter volume, neurogenesis, synaptic plasticity, and blood flow.⁵⁸¹ Child maltreatment has been associated with decreased hippocampal volumes in adults.⁸⁶⁷ Further research is needed to evaluate whether physical activity interventions can reverse this change.

Physical activity is associated with improved memory and attention, cognition, academic achievement, and psychosocial functioning; however, studies are not uniform in the type, intensity, or frequency of exercise needed to achieve these outcomes.^{581,754} A meta-analysis of 36 studies, including 12,820 total records of adults over 50 years, found that 45 to 60 minutes of at least moderate-intensity physical exercise improved cognitive function (effect size, or group difference, of 0.29).⁸⁶⁸ Improvements in mental health and pain perception associated with exercise may be due to increasing dopamine and endogenous opioid levels.⁷⁵⁴

Endocrine impacts

Physical activity itself can represent a physiologic stressor, and can stimulate the acute stress response, activating the HPA axis and the SNS.⁸⁶⁹ Thus, it is not surprising that physical activity is associated with increases in cortisol, catecholamines, and growth hormone.⁸⁶⁹ Increases in cortisol can occur in endurance and resistance exercise, but more so with vigorous or high-intensity physical activity.⁸⁶⁹ In a study of 12 endurance-trained males who cycled at low, moderate, or high intensity, cortisol levels increased significantly only in response to high-intensity exercise.⁸⁷⁰

Other key changes in hormone levels can occur during exercise. Epinephrine levels generally increase with physical activity, while studies are mixed as to the norepinephrine response.⁸⁶⁹ Growth hormone increases immediately with endurance or resistance exercise and decreases when activity stops.⁸⁶⁹ Nutrition, sleep, gender, prior exercise, physical fitness, environmental conditions, exercise intensity, and duration can all affect the magnitude of growth hormone release.⁸⁶⁹ Insulin levels decrease during exercise, allowing for greater glucose production and release to prevent hypoglycemia.⁸⁶⁹

There seems to be a paradox: exercise can elicit the stress response, but it also confers many health benefits. There are a number of possible explanations. First, some stress is helpful and can build protective immunity, increase mental and physical performance, and improve health and well-being.⁸⁷¹ Thus, physical activity may promote improved regulation of the stress response and a shift toward the positive stress response, and away from toxic stress.⁸⁷² Physical activity may also help metabolize the increased energy associated with anxiety or perceived (but not actual) threats. For example, a child who has experienced ACEs and is hyper-aroused and hypervigilant at school may be more activated by perceived threats and have trouble sitting still. Brief physical activity breaks may help the child release the excess energy and regulate the threat-response system.

Immune impacts

Physical activity has been associated with overall improved immune system function.^{754,873} A single bout of moderate to high-intensity exercise has been

associated with increased immune cell counts and cytokine levels during exercise and decreased lymphocytes and antibody response for a period after exercise.⁸⁷⁴ This may lead to a general anti-inflammatory effect of regular exercise over time.⁸⁷⁵ The reductions in immune cell counts after exercise have also been associated with immune cell mobilization, heightened immune surveillance, and increased immune system regulation, leading to the potential for enhanced overall immune competency across the lifespan.⁸⁷⁶ While intense, long-duration, elite-level physical activity has been associated with immune suppression and increased infection risk, moderate-intensity exercise has been associated with decreased upper respiratory tract infections.^{875,877}

Additional mechanistic pathways

Physical activity may help individuals affected by ACEs by increasing resilience factors such as skill development, self-regulation, problem-solving abilities, and a sense of agency.^{878,879} Physical activity may also support healthy relationships. For adolescents, team sport participation has been shown to decrease the odds of receiving a diagnosis of depression (aOR 0.76), having current depressive symptoms (aOR 0.85), or anxiety (aOR 0.70). Stratified analysis found similar results among males; however, for females, team sport participation was associated only with decreased anxiety.⁸⁸⁰ Exercise can improve sleep, which can also improve immune function.⁷⁵²

Physical activity, hormones, obesity, and weight loss

A large review by Hansen and colleagues found that cortisol levels may increase more in obese individuals than in lean individuals following exercise, while epinephrine and growth hormone release may be lower.⁸⁶⁹ It is hypothesized that the lower epinephrine levels may be due to a blunted SNS response.⁸⁶⁹ Unfortunately, rates of fat breakdown (lipolysis) are also lower in obese subjects, which may be related to the decreased growth hormone levels.⁸⁶⁹ In addition, hyperinsulinemia is more likely to persist in obese individuals during and after exercise, further blunting fat breakdown.⁸⁶⁹ Taken together, these findings suggest that weight loss and stress relief through physical activity may be more difficult for obese individuals than for lean individuals. There is also limited data on whether long-term exercise alone can reverse these hormonal changes for obese individuals.⁸⁶⁹

Interventions

- Moderate-intensity aerobic exercise three times a week for a minimum of nine weeks has been shown to improve depression.⁸⁸¹
- Low mood and stress have been identified as barriers to exercising; professional support may help patients overcome these barriers.⁸⁸²

- Among patients with PTSD, physical activity may reduce depressive symptoms, PTSD symptoms, anxiety, and stress.⁸⁸³
- Physical activity interventions for anxiety were more effective when they included supervised exercise, moderate- or high-intensity exercise, and exercise at a fitness center rather than at home.⁸⁸⁴
- Programs that couple physical activity with self-regulation skills, such as martial arts and yoga, may lead to more improvements in executive functioning.⁸⁸⁵
- Gamification strategies, such as the Behavioral Economics Framingham Incentive Trial, which gamified step goals, can help improve activity levels.⁸⁸⁶

Overall, physical activity is a valuable tool in helping to mitigate the health consequences of ACEs and toxic stress. Medical providers can discuss the stress-related health benefits of physical activity, identify strategies to support moderate-intensity aerobic exercise, and suggest team sports, fitness centers, supervised individual or group activities, and/or combined practices such as yoga or martial arts.

KEY TAKEAWAYS: PHYSICAL ACTIVITY

- > Physical activity is associated with improved memory and attention, cognition, academic achievement, psychosocial functioning, and immune function.
- > Physical activity may help promote the positive stress response, metabolize increased energy associated with anxiety or stress, and increase resilience factors.
- > Physical activity may also support healthy relationships—for example, through coaching and team sport participation.
- > Brief physical activity breaks may help release excess energy and regulate the threat-response system.
- > Moderate-intensity aerobic activity, for longer durations, at a frequency of three times or more a week, has been associated with improved health outcomes.
- > Activities that combine physical activity with self-regulation skills and breathing techniques, such as martial arts and yoga, may also be beneficial.
- > Low mood and stress have been identified as barriers to exercising; professional support may help patients overcome these barriers.

MINDFULNESS PRACTICES

Complementary and alternative medicine (CAM) use is common in the United States, with a 2007 study finding that 40% of adults and 11% of children had used such therapies within the past 12 months.⁸⁸⁷ In adults, the most commonly used CAM therapies were non-vitamin, non-mineral natural products, deep-breathing exercises, meditation, chiropractic or osteopathic manipulation, massage, and yoga.⁸⁸⁷ While the evidence is strongest for mindfulness and meditation, an expanding body of literature has indicated that other approaches, including yoga, acupuncture, breathing techniques, and neurofeedback, may be promising practices to support healing from ACEs and toxic stress.⁸⁸⁸⁻⁸⁹⁴

Mindfulness has been defined as nonjudgmental, moment-to-moment awareness that involves attention, intention, and a kind attitude.^{889,895,896} Mindfulness originates in ancient Buddhist practices; however, secular versions, including mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy, are increasingly used to reduce stress and improve health.^{889,897} MBSR is an eight-week program with weekly two-and-a-half-hour in-person (and now also virtual) sessions with daily home practice; it was originally designed to support cancer patients but has been adapted for general use and implemented across the country.⁸⁸⁹ Shapiro and colleagues refer to a process of “re-perceiving” in which mindfulness produces a shift in perspective that allows for more flexibility in behaviors.⁸⁹⁶ Mindfulness may increase the space between perception of threat and one’s response, as described by Holocaust survivor and psychologist Viktor Frankl: “Between stimulus and response, there is a space. In that space lies our freedom and our power to choose our response. In our response lies our growth and our happiness.”⁸⁹⁸

A rapidly growing body of research shows that mindfulness practices can support trauma healing and regulation of stress, emotions, and behavior for children^{726,755,899-904} and adults.^{726,756,897,905-910} Mindfulness has been shown to be helpful for people with ACEs and trauma,⁷²⁶ PTSD,⁷²⁶ anxiety and depression,^{726,897,905,906,911-913} executive functioning disorders,^{726,912,914} pain management concerns,^{897,915} attention-deficit/hyperactivity disorder (ADHD),⁹¹⁶ sleep problems,^{917,918} and parental stress.⁷²⁶ It has also been shown to decrease shame and increase acceptance, self-compassion,^{919,920} and empathy.^{921,922} Mind-body therapies improve mental health problems,^{902,923} including depression and anxiety.⁹²⁴

Mechanisms

The literature is still emerging; however, the science suggests that mindfulness may support trauma healing via regulation of the stress response^{755,756} and improved functionality and connectivity among regions of the brain involved in attention, self-referential thinking, and emotional regulation.^{726,912,914,925,926} Mindfulness may offer

cognitive and behavioral flexibility in the face of stressful events and increase one's ability to tolerate uncomfortable emotions.^{896,897}

Neuroendocrine impacts

Functional magnetic resonance imaging (fMRI) studies suggest that mindfulness involves the brain's frontal regions, primarily the medial frontal cortex, including the anterior cingulate cortex, as well as the cortical midline structures, insula, amygdala, and the hippocampus.⁹²⁶ Mindfulness may act on the attention networks in the brain and improve the default mode network processes, thus supporting self-referential thinking.^{925,926}

From a stress-reduction perspective, mindfulness has been associated with decreased cortisol levels, although there have been some conflicting reports.⁸⁹⁷ In one study, 38 adults were evaluated before and after a three-month yoga/meditation retreat and on average, were found to have decreased depression and anxiety, increased BDNF, and increased morning cortisol.⁹²⁷ Mindfulness has also been associated with decreased sympathetic activation, lower blood pressure,⁸⁹⁷ and improved parasympathetic activity, with increasing heart rate variability.⁹²⁸ Many studies have linked mindfulness programs with self-reported decreases in stress levels and in maladaptive responses to stress.^{726,755,929-931}

Cardiovascular disease

Transcendental meditation (TM) was associated with decreased carotid atherosclerosis in Black Americans with hypertension (compared to those who received only health education)⁹⁰⁹ and reduced exercise-induced myocardial ischemia in patients with coronary artery disease.⁹³² In a study of 201 Black men and women with coronary artery disease, TM was associated with a reduced risk of mortality, myocardial infarction, and stroke, and these changes were found in association with lower blood pressure and psychosocial stress factors.⁹³³

Immune function

Mindfulness has been associated with improved immune function.^{726,897,907} A meta-analysis suggests that mindfulness can influence markers of inflammation, cell-mediated immunity, and biological aging. However, there is substantial heterogeneity across studies and the need for more research.⁹³⁴

Interventions

As always, interventions can start as self-care for providers. Mindfulness has been found to decrease provider stress and burnout,⁹³⁵⁻⁹³⁸ improve patient-centered care,^{939,940} increase empathy,⁹⁴¹ improve patient satisfaction,⁹⁴² and reduce implicit bias.⁹⁴³ Mindfulness is also associated with decreased parental stress and an

improved caregiver-child relationship.⁷⁵⁵

The American Heart Association reports that, given the low costs, low risks, and potential benefits, meditation could be considered an adjunct to routine treatments for cardiovascular disease.⁹¹⁰ Use of online and downloadable apps for mindfulness has been demonstrated to improve stress, resilience, and mental health symptoms^{922,944} and is associated with lower blood pressure.⁹⁴⁵

As noted above, other mind-body practices, including tai chi, yoga, acupuncture, breathing techniques, massage therapy, and neurofeedback, show promise to support healing from ACEs and toxic stress.^{752,805,888-894,946} Discussions combined with motivational interviewing techniques can help determine which practice might best support each patient.

KEY TAKEAWAYS: MINDFULNESS PRACTICES

- > Mindfulness has been defined as nonjudgmental, moment-to-moment awareness that involves attention, intention, and a kind attitude.
- > Mindfulness has been shown to be helpful for people with ACEs and trauma, PTSD, anxiety and depression, executive functioning issues, pain management issues, ADHD, sleep problems, and parental stress.
- > Research shows that mindfulness practices can support trauma healing and regulation of stress, emotions, and behavior for children and adults.
- > Mindfulness has been shown to decrease shame and increase acceptance, self-compassion, and empathy.
- > Mindfulness has been associated with improved cardiovascular and immune health.
- > Mindfulness has been found to decrease provider stress and burnout, improve patient-centered care, increase empathy, improve patient satisfaction, and reduce implicit bias.
- > Mindfulness also decreases parental stress and improves the caregiver-child relationship.
- > Mindfulness-based stress reduction (MBSR) is an eight-week program with weekly sessions and daily home practice. Programs are available through work wellness programs, hospitals, community organizations, and online.
- > Online and downloadable apps for mindfulness are also available.
- > Other mind-body practices, including tai chi, yoga, acupuncture, breathing techniques, massage therapy, and neurofeedback, can also support healing from ACEs and toxic stress.

EXPOSURE TO NATURE

Nature can come in many forms, including local, state, or national parks, green spaces around work or school environments, playgrounds, and even indoor plants. Importantly, access to natural environments can improve health.

Interacting with nature is associated with decreased diabetes, depression,⁹⁴⁷ heart rate and blood pressure,⁹⁴⁸ heart disease,⁹⁴⁹ and mortality.^{948,950-952} Walkable green space in a city was associated with longer life for senior citizens in Tokyo.⁹⁵³ In a randomized controlled study of 90 patients recovering from surgery, plants and flowers in the hospital rooms were associated with lower blood pressure, lower ratings of pain, anxiety, and fatigue, and higher room satisfaction.⁹⁵⁴ Similarly, patients who had a room with a view looking out on a natural scene had shorter hospital stays and required less pain medication.⁹⁵⁵

Adding green spaces in low-resourced communities has been associated with reduced crime and violence, improved perception of safety, increased social connections, and reduced depressive symptoms.^{947,956,957} Conversely, losing trees has been associated with increased crime and worse health, including increased cardiovascular and respiratory deaths.^{952,957,958} Nature most likely improves health for children and adults with toxic stress by directly calming the stress response system, as well as by increasing healthy behaviors such as physical activity, mindfulness, and relational health. Parks and exposure to nature have been shown to increase play and physical activity, and to decrease screen time.⁹⁵⁹ Nature may also increase opportunities for relationship and connection and improve sleep.^{757,758} Studies also document improvement in family functioning and attachment,^{757,960} and increase in social ties.⁷⁵⁸

A study of park prescriptions at a pediatric primary care clinic in a city found that they increased park visits and physical activity, and were associated with decreased perceived stress, loneliness, and cortisol levels.⁷⁵⁷ Another study by the same author found that counseling children and families about nature was associated with greater time spent in nature and decreased parental stress.⁷⁵⁷ Time in nature has been associated with decreased SNS activity and increased parasympathetic nervous system activity.⁷⁵⁸ Nature has also been linked to decreased blood glucose levels and reduced inflammatory cytokines and NK cells.⁷⁵⁸ A small study of 30 subjects found that images of urban scenery were associated with activation of the hippocampus and amygdala (both of which are involved in stress pathways), while rural scenery images were associated with activation of the anterior cingulate, globus pallidus, putamen, and caudate nucleus (involved in empathy, impulse control, and proprioception pathways).⁹⁶¹

Interacting with nature may improve cognitive functioning and attention.^{758,960,962} In a study of 547 adults, connectedness to nature was associated with improved psychological well-being, meaningfulness, and energy.⁹⁶³ Another study had 12 students wear mobile devices that recorded brain electrical activity (via an EEG), and walk through three different neighborhoods in Edinburgh: a populated, urban shopping district, a path through trees and fields, and a busy commercial district.

Transitioning from the shopping district to the green space was associated with decreased arousal and frustration, and an increase in brain electrical patterns associated with a meditative state.⁹⁶⁴

Access to nature is, unfortunately, not equal. Low-income neighborhoods often have fewer trees, parks, and green spaces.^{959,965,966} In a study of 890 caregivers at an urban pediatric federally qualified health clinic, 17% felt that “access to green spaces/parks/playgrounds” was an unmet social need.⁹⁶⁵ In addition, the study found significantly increased odds that access to nature was an issue for families living at or below the poverty line.⁹⁶⁵ This social inequality in access to green space may be a mechanism by which disadvantaged communities experience poorer outcomes in the face of high stress and adversity. In addition, adversity is demonstrated to interact with air quality, resulting in poorer lung function for children in high-stress environments for a given level of air pollution.⁹⁶⁷ Similarly, a study done in northwest Florida found that stroke mortality was associated with lower incomes, increased pollution, and decreased green space.⁹⁶⁸

The experience of being in nature is also not the same for all populations. Both current and historical racism within park systems and natural spaces have contributed to feelings of lack of safety and inclusion for some communities of color.⁹⁶⁹ Historically, “redlining” policies forced minorities to live in locations that often had less green space.⁹⁷⁰ Extra efforts must be made to support historically marginalized communities, including Black and other minority Americans, in feeling safe and welcome in nature.

There are many ways that nature has been used as a therapeutic modality, including nature prescriptions, wilderness therapy, adventure-based programs, and ecotherapy.

Tools for improving nature usage and access

- Providers can discuss the important link between health and nature and encourage time in nature as a health intervention.
- Park prescriptions can be used in primary care clinics as a way to start a conversation about nature, encourage park usage, and demonstrate the link between nature and health; see parkrx.org.⁹⁷¹
- Hospitals, schools, and workplaces may be encouraged to increase indoor and outdoor green space.
- Providers can recognize that there may be cultural, community, and policy barriers to equal access to nature. Access to nature is a social justice health issue.
- Patients may be referred to ecotherapy, wilderness therapy, or adventure-

based treatment programs.

KEY TAKEAWAYS: EXPOSURE TO NATURE

- > Nature can come in many forms, including parks, local green spaces, playgrounds, and even indoor plants.
- > Access to these natural environments can improve health.
- > Adding green spaces in low-resourced communities has been associated with reduced crime and violence, improved perception of safety, increased social connections, and reduced depressive symptoms.
- > Interacting with nature is associated with decreased diabetes, depression, heart rate, blood pressure, and mortality.
- > Nature is associated with calming the stress response system and increasing healthy behaviors such as physical activity, mindfulness, and relational health.
- > Social inequality in access to green space may be a mechanism by which disadvantaged communities experience poorer outcomes in the face of high stress and adversity.
- > Both historical and current racism within park systems and natural spaces as well as “redlining” practices have contributed to feelings of lack of safety and inclusion for some communities of color. Extra efforts must be made to support Black Americans and other minorities in feeling safe and welcome in nature.
- > Providers may encourage time in nature as a health intervention.
- > Increased indoor and outdoor green space should be encouraged.
- > Providers may consider park prescriptions, ecotherapy, wilderness therapy, or adventure-based treatment programs.

MENTAL AND BEHAVIORAL HEALTHCARE

Individuals requiring mental health and substance abuse services represent a special population with particularly high risk for ACE exposure and toxic stress.^{972,973} Mental and behavioral healthcare can help patients build skills and capacities for resilience, directly address trauma-related symptoms, and scaffold with medications as necessary, all in the context of safe, supportive, and trusting relationships.⁹⁷³ Integrated primary care and behavioral health and team-based care represent clinical best practices for addressing the range of outcomes associated with toxic stress. Multidisciplinary teams may include primary care providers, mental or behavioral health providers, care coordinators and navigators, social workers, or others, such as peer supports. This section offers an introduction to the various aspects of mental and behavioral healthcare that can support healing from toxic stress.

It is important for mental and behavioral health systems to be trauma-informed and include a recognition of the science of ACEs and toxic stress. Multidisciplinary care should include bidirectional flow of information, as ACEs are risk factors not only for mental and behavioral but also for non-neuropsychiatric health conditions. Just as primary care providers may refer patients in need to a mental or behavioral health provider, so too can mental and behavioral health providers who, in the course of treatment, learn of a patient's history of ACEs or other risk factors for toxic stress, can encourage and/or refer patients to seek trauma-informed care for other AAHCs. Increased communication across disciplines, integration of services, and shared treatment plans can improve access and care for individuals with high risk of toxic stress.

There is a vast body of literature linking various behavioral and mental health therapies with improved outcomes, and summaries of best practices can be found in the National Academies of Sciences, Engineering, and Medicine's report, *Fostering Healthy Mental, Emotional, and Behavioral Development in Children and Youth: A National Agenda*, the US Surgeon General's Report, *Addiction in America*, and resources from the [National Child Traumatic Stress Network \(NCTSN\)](#), the [Substance Abuse and Mental Health Services Administration \(SAMHSA\)](#), and the [California Evidence-Based Clearinghouse for Child Welfare \(CEBC\)](#).⁹⁷⁴⁻

⁹⁷⁸ As with treatment of other AAHCs, the treatment approach for mental and behavioral sequelae of toxic stress should incorporate strategies to mitigate the toxic stress response. There is not yet sufficient evidence to determine whether mental health interventions are warranted for patients at intermediate or high risk of toxic stress, but who do not have mental or behavioral symptoms. Few cross-disciplinary research studies have addressed whether these therapies are reliably associated with clinical improvement of physical health outcomes. The limited research available, however, does indicate that psychological interventions can improve both the mental and the physical health consequences of toxic stress.^{603,759,979} Continued multidisciplinary research in this area should be a priority.

A recent Cochrane review evaluated psychological interventions for parents of children and adolescents with chronic illnesses, and while there were a limited number of high-quality studies, CBT for the parents showed promise in decreasing children's medical symptoms.⁹⁸⁰ The Creating Opportunities for Personal Empowerment (COPE) for Asthma program, which incorporated cognitive-behavioral skills-building for children with asthma and anxiety, found reductions in self-reported symptoms of anxiety and increased child management self-efficacy and asthma illness representations.⁹⁸¹

In a randomized controlled trial of 437 adults with recently diagnosed heart disease, patients who received traditional care plus CBT had a 41% lower rate of a

Therapy	Ages	General Description
<u>Child-Parent Psychotherapy</u>	Birth to 6 years	Dyadic intervention for young children and their caregivers that supports family strengths and relationships. ^{586,587,994}
<u>Parent-Child Interaction Therapy</u>	2 - 12 years	Dyadic parent training treatment that emphasizes improving the quality of the parent-child relationship and interactions. ⁹⁹⁵⁻⁹⁹⁷
<u>Cue-centered therapy</u>	8 - 18 years	Protocol of 15 sessions through which children and caregivers learn about traumatic stress, how to cope rather than avoid, and the value of verbalizing their life experiences. ^{998,999}
<u>Trauma-focused cognitive behavioral therapy (TF-CBT)</u>	Verbal children and adults	A structured, short-term treatment model for children and adults who have experienced trauma. ¹⁰⁰⁰⁻¹⁰⁰²
<u>Eye movement desensitization reprocessing (EMDR)</u>	Verbal children and adults	Focuses on helping clients resolve unprocessed traumatic memories. ¹⁰⁰³⁻¹⁰⁰⁵
Family systems therapy	Verbal children and adults	Supports resolving family conflict or issues. ^{1006,1007}
Cognitive processing therapy	Adolescents and adults	A type of CBT, generally 12 sessions, that helps modify maladaptive thinking related to their trauma. ¹⁰⁰⁸
Prolonged exposure therapy	Adolescents and adults	A CBT approach that helps clients gradually approach their memories, feelings, and situations of trauma. ¹⁰⁰⁹

Evidence-based trauma therapies.

recurrent cardiovascular disease event and 45% fewer heart attacks than patients who received traditional care alone.⁹⁸²

Neuro–endocrine–immune–metabolic function

CBT is based, at least in part, on the concept that thought can influence emotions and behavior. Thus, CBT may help improve patient awareness of negative thoughts, behaviors, and feelings about their disease, increase compliance with medical recommendations, and support healthy self-care behaviors.⁹⁸³ Cognitive therapy may enhance prefrontal cortex function and inhibit amygdala activation.⁹⁸⁴ A study of both trauma-focused cognitive-behavioral therapy (TF-CBT) and eye movement

desensitization and reprocessing (EMDR) found improvements in PTSD symptoms correlated with alterations in bilateral temporal lobe connectivity.⁹⁸⁵

A systematic review found that psychosocial interventions for children were associated with improved cortisol regulation.⁷⁵⁹ Boparai and colleagues found that a number of behavioral and mental health interventions, including Attachment and Biobehavioral Catch-Up (ABC), Strong African American Families (SAAF), and CPP, were associated with improvement in various markers of neuro-endocrine-immune-metabolic regulation, including cortisol, epigenetic regulation, and brain development.⁶⁰³ CPP has also been found to be effective in treating depression and PTSD, decreasing stress, and improving self-efficacy in both parents and children with high ACE scores.^{96,586,587,699,986} CPP has also been shown to protect against the telomere shortening associated with trauma, suggesting the intervention slowed, stopped, and, for some children, reversed the cellular “wear and tear” of early adversity.⁴⁹²

Who needs therapy?

Generally, individuals who have trauma-related mental or behavioral health symptoms (e.g., depression, anxiety, anger management concerns, and alcohol or other substance misuse or dependence) should be offered evidence-based and trauma-appropriate mental or behavioral health services. Mental health therapy can be used in combination with the other strategies for toxic stress mitigation. Of note, routine mental health referrals for all patients who have experienced ACEs are not recommended or indicated by current evidence. Those who manifest non-neuropsychiatric manifestations of toxic stress, such as immunologic, inflammatory, cardiovascular, or metabolic conditions, may benefit from mental health interventions. However, more research is needed.

Trauma therapy

Just as in other fields, mental health practitioners have specialties and can be trained and certified in various mental health modalities. It is important to help individuals who have experienced ACEs connect with therapists who can provide trauma-focused services. Trauma-trained mental health practitioners should have certification or expertise in at least one of the evidence-based trauma therapies.

Given that the client-therapist relationship is critical to helping establish new patterns of trust and safety, individuals interested in mental health therapy are encouraged to interview therapists before starting therapy. Similarly, if therapy does not seem to be helping, one should consider trying a different therapist or different treatment modality before giving up on mental health therapy altogether.

The CEBC and the NCTSN both offer searchable databases of mental health

therapies. Below are a few examples of evidence-based therapies demonstrated to support healing for children and adults affected by trauma and toxic stress.^{725,987-993}

Developmental and behavioral pediatrics (DBP)

Pediatricians specializing in DBP have broad expertise in developmental and behavioral assessments and in supporting children and families address identified concerns. DBP can support multidisciplinary care and offer evidence-based strategies and interventions to help children with ACEs and toxic stress.¹⁰¹⁰

Psychiatry

Psychiatrists can provide critical support for children and adults with severe trauma symptoms, especially when they understand the biology of toxic stress. For children, it is important that psychiatrists recognize the developmental consequences of trauma, can differentiate trauma from oppositional defiant disorder or ADHD, and are sensitive to issues of polypharmacy.⁷⁰⁴

Medications

Medications can be important adjunctive treatment for addressing the sequelae of ACEs and toxic stress. It is important for prescribing clinicians to consider how medications might best be utilized in concert with other treatment modalities (including all stress mitigation strategies) that will ultimately lead to sustained healing. Monitoring and avoiding polypharmacy are especially important in at-risk groups such as children in foster care.

Medications for mental health diagnoses are often prescribed by primary care providers, given limitations in access to psychiatry support; however, advocacy and public policy efforts should be made to ensure adequate access to all forms of mental health support, including psychiatry.

- Selective serotonin reuptake inhibitors (SSRIs) are a class of antidepressants that may be helpful in the treatment for acute stress disorder, non-combat PTSD (such as motor vehicle accidents, childhood and adult sexual assault, and other interpersonal traumas), and associated anxiety and depression.¹⁰¹¹
- There are no drugs, including antidepressants, that have been found to specifically treat PTSD symptoms in children.¹⁰¹²⁻¹⁰¹⁶
- Prazosin, an α -1 adrenergic antagonist, is a promising treatment option for PTSD-related nightmares and sleep disruptions for adults and children.^{1011,1017}
- Clonidine and guanfacine are alpha-2 agonists that may help children and adults with intrusive and hyperarousal symptoms associated with PTSD.^{1018,1019} For traumatized youth and adults, guanfacine may help calm the fight-flight-or-freeze response while enhancing prefrontal cortex inhibition of the

amygdala.^{1018,1019}

- Psychiatric medications are thought to act primarily by altering neurotransmitters such as dopamine and serotonin within the brain, but emerging research shows they may also support healing by improving autonomic nervous system regulation¹⁰²⁰ and immune system regulation.⁷⁵²

Access to mental healthcare

A 2018 online survey of 5,000 Americans found that while the need for mental health services is high (over half of respondents considered or sought mental health services), access to care (not quality of care) was the biggest hurdle in addressing mental health needs.¹⁰²¹ Access is an even greater barrier for Black, Latinx, and Asian Americans.¹⁰²² The cost of mental health services can also be a barrier to care, especially for those who are uninsured or privately insured.^{1023,1024}

Engagement in therapy

Many people who are referred to mental health therapy do not initiate or maintain services, and racial/ethnic minorities are much less likely (by 20-50%) to engage in mental health services.¹⁰²⁵ Barriers to starting and staying in therapy include access, transportation issues, fear of stigmatization, uncertainty of what to expect, lack of culturally and linguistically congruent providers for racial/ethnic minorities, and length of wait until first appointment.¹⁰²⁶⁻¹⁰²⁸ For children and adolescents, contributing factors included family attitudes, flexibility and availability of services, stigma, and degree of coordination and integration of care.¹⁰²⁹ Both outreach and integrated care have been found to improve engagement.¹⁰²⁹ A focus on the therapeutic alliance, person-centered care, peer support, and culturally and linguistically congruent care are also important.^{1028,1030} Care coordination, navigators, and integrated behavioral health services can also help improve engagement and access to care.¹⁰³¹

CULTURAL COMPETENCE

Cultural competence includes framing mental health services in culturally relevant ways, allowing for complexity of issues based on culture, gender, class, national origin, and race, being respectful of cultural preferences around personal space and touch (such as hugging), recognizing cultural issues around power and control, and interpreting mental health symptoms and emotions in the context of culture. While cultural competence has been used to describe an approach or skill set for understanding another person's culture, cultural humility recognizes that one may never fully understand another's culture and offers a framework for personal accountability, ongoing learning, and challenging of barriers that impact marginalized communities.

Cultural considerations

Addressing cultural competence, sensitivity, and humility must be an individual practice, as well as a priority for improving systems and policy more broadly. Linguistic and cultural congruence between provider and patient is critical in addressing health equity and highlights the need to advance a more culturally and linguistically diverse mental health provider workforce.¹⁰²⁸ **Cultural competence** includes framing mental health services in culturally relevant ways, allowing for complexity of issues based on culture, gender, class, national origin, and race, being respectful of cultural preferences around personal space and touch (such as hugging), recognizing cultural issues around power and control, and interpreting mental health symptoms and emotions in the context of culture.¹⁰³² While cultural competence has been used to describe an approach or skill set for understanding another person's culture, cultural humility recognizes that one may never fully understand another's culture and offers a framework for personal accountability, ongoing learning, and challenging of barriers that impact marginalized communities.¹⁰³³ A systematic review of models for professional training on cultural competence among mental health practitioners found that none of the studies evaluated patient experience and outcomes.¹⁰³⁴ Thus, it is important for individual patients and referring clinicians to identify mental and behavioral health providers who demonstrate cultural sensitivity and humility. Further, on a systems level, there is a need to increase parity and leadership of underrepresented minorities in the mental health workforce.

Integrated behavioral health models

For patients with neuropsychiatric symptoms, integrating behavioral and mental health with primary care improves outcomes and is a critical element in addressing toxic stress physiology.¹⁰³⁵ Studies have shown that integrated services can decrease healthcare utilization,⁵⁵² and improve mental and behavioral health outcomes, including depression, panic disorder, substance dependence, chronic pain, and medication adherence.¹⁰³⁶ A meta-analysis of 31 studies with over 13,000 patients found that integrated care improved behavioral health outcomes.¹⁰³⁵ A more recent meta-analysis of integrated care models for children found improved quality of life and cost savings compared to usual care.¹⁰³⁷ Further multidisciplinary research is needed to explore how integrated behavioral health may improve physical health outcomes.

Care coordination and care management

Care coordination is a team-driven activity that can help organize and integrate services as well as support children and adults navigating across clinics, health systems, and services.¹⁰³⁸ The Center for Health Care Strategies and the Agency for

Healthcare Research and Quality define care management this way:

“Care management programs apply systems, science, incentives, and information to improve medical practice and assist consumers and their support system to become engaged in a collaborative process designed to manage medical/social/mental health conditions more effectively. The goal of care management is to achieve an optimal level of wellness and improve coordination of care while providing cost effective, non-duplicative services.”¹⁰³⁹

A study found that the medical home model, including having a personal provider, a usual source for medical care, family-centered care, and having effective care coordination, was associated with improved child well-being (as measured by the child well-being index).¹⁰⁴⁰ A study of 11 high-income countries (Australia, Canada, France, Germany, the Netherlands, New Zealand, Norway, Sweden, Switzerland, United Kingdom, and the United States), demonstrated that the United States lags behind the other nations in care coordination, with almost one in 10 adult patients reporting poorly coordinated care.¹⁰⁴¹

Substance abuse

The treatment of substance use disorder is greatly enhanced when comorbid mental health problems are simultaneously addressed.¹⁰⁴² Studies have shown that adding trauma-focused therapy to substance use disorder treatment can improve outcomes.¹⁰⁴³⁻¹⁰⁴⁵ SAMHSA has developed in-depth toolkits for understanding, implementing, and integrating treatment for trauma, traumatic (or toxic) stress, and substance abuse.^{1046,1047}

KEY TAKEAWAYS: MENTAL AND BEHAVIORAL HEALTHCARE

- > Mental and behavioral healthcare can help patients build skills and capacities for resilience, directly address trauma-related symptoms, and scaffold with medications as necessary, all in the context of a safe, supportive, and trusting clinical relationship.
- > Mental and behavioral health systems should be trauma-informed and include a recognition of the science of ACEs and toxic stress.
- > Mental and behavioral health providers who, in the course of treatment, learn of a patient's history of ACEs or other risk factors for toxic stress, can encourage and/or refer patients to seek trauma-informed care for AAHCs.
- > Multidisciplinary care should include bi-directional flow of information as high ACEs are a risk factor for numerous mental, behavioral, and physical health conditions.
- > Studies suggest that behavioral and mental health programs can improve physical health and neuro-endocrine-immune-metabolic dysregulation; however, more multidisciplinary research is needed.
- > Individuals who have trauma-related mental or behavioral health symptoms (e.g., depression, anxiety, anger-management concerns, and alcohol or other substance misuse or dependence) should be offered evidence-based and trauma-appropriate mental health services.
- > Limited access to mental healthcare is a serious issue in the United States. Barriers are even greater for Black, Latinx, and Asian Americans.
- > The cost of mental health services can also be a barrier to care, especially for those who are uninsured or privately insured.
- > Multidisciplinary teams, integrated behavioral and mental healthcare within the primary care setting, care coordination, and medical home models may help address some barriers to care.
- > Linguistic and cultural congruence between provider and patient is critical in addressing health equity and highlights the need to advance a more culturally and linguistically diverse mental health provider workforce.
- > Medications for mental health issues are often prescribed by primary care providers, given the limited access to psychiatry support; however, public policy efforts should be made to ensure adequate access to all forms of mental health support, including psychiatry.

MANDATED REPORTING

The goal of ACE screening and trauma-informed care is to identify risk and protective factors before a reportable event occurs, and provide support, scaffolding, coping strategies, and stress buffering skills to prevent future ACEs. However, ACE screening may uncover active or recent neglect or abuse that must be reported to Child Protective Services (CPS) or law enforcement to ensure the safety of a child. While a mandated report will most likely cause stress for the patient and the provider, it is important to remember:

1. Not all positive ACE screens require mandated reporting. Further

discussion with the patient and family are needed to further assess. If in doubt, a provider can call the CPS hotline and receive guidance as to whether a report is required.

2. Addressing the safety needs of the child can protect the child from further harm.
3. Not all CPS reports result in removal. In 2018, nationally, CPS received approximately 4.3 million referrals (regarding 7.8 million children), and approximately 150,000 children received foster care services.¹⁰⁴⁸
4. CPS and law enforcement can offer additional services to support the child and family. Differential response is an example of a CPS program that offers resources and supports to the family.
5. A trauma-informed approach to mandated reporting can lessen the stress and even bolster the patient-provider relationship through the process.

Applying the principles of trauma-informed care to mandated reporting can help decrease some of the uncertainty and loss of control associated with the process.^{1049,1050}

1. **Safety.** Provide a private and safe space for the patient to disclose and discuss next steps. The clinician taking a few moments or deep breaths, if needed, can be helpful to achieve a state of being calm and reassuring for the patient. Of note, the clinician doesn't need to get all the details of the adverse event, just enough information to know whether there is a suspicion of neglect or abuse. CPS and/or law enforcement will hopefully arrange for a formal forensic interview to get details in a professional and trauma-informed manner. It is ideal to have a mental health provider or social worker involved in supporting the patient through the process.
2. **Trustworthiness and transparency.** Provide information about the process of reporting and give clear indications of what to expect. Explain confidentiality around the process and who may or may not find out. The CPS hotline worker is a good resource about some of these aspects of confidentiality and process to report back to the patient.
3. **Peer support.** Offer to connect the patient to an advocate on the phone or support group.
4. **Collaboration, empowerment, voice, and choice.** Depending on the age of the patient and the situation, consider offering to let the patient listen to and be part of the call to report. Ask if they would like anyone else to be with them for any part of the discussion or the call itself.
5. **Attention to cultural, historical, and gender issues.** It is important to

consider cultural and historical differences in parenting styles and customs when considering a suspicion of abuse and neglect. It is also important to recognize that boys and men can be sexually abused, that women can be perpetrators, and that lesbian, gay, bisexual, and transgender children are at increased risk for neglect and abuse.^{15,1051-1054}

CONCLUSION

There are a number of evidence-based and promising tools, strategies, interventions, and treatment measures that can help support children and adults identified as being at intermediate or high risk for toxic stress. Primary care providers can use strategies for buffering the toxic stress response—relational health, sleep, nutrition, physical activity, mindfulness, access to nature, and mental and behavioral health—to offer assessment, patient education, specific intervention strategies, and referrals for patients at increased risk. This is an integrated, bio-psycho-social approach that allows for multidisciplinary treatment efforts.

ACE screening involves assessing for the triad of *adversity* (ie, ACE score), clinical manifestations of *toxic stress* (ie, AAHCs), and *protective factors*.⁶⁹⁹ Many tools have been presented throughout this section that can be used to assess for strengths and protective factors within each of the stress-buffering strategies. Within each strategy, intervention and referral suggestions are also offered that the primary care provider can use in conjunction with mental health providers and/or community supports. Health plans and providers should work to identify local resources that are available for referral for ACEs prevention and toxic stress mitigation, as well as to address additional social determinants of health such as housing and food insecurity. As a starting point, clinic administrators and staff can inquire with health plans as to whether any community organizations may already be involved in such efforts, such as through Medi-Cal's Whole Person Care pilots and/or the Health Homes Program. Additional guidance related to the state's efforts toward supporting a Network of Care around ACE screening and response is forthcoming. Tools such as such as [Aunt Bertha](#), [FINDConnect](#), and [ONE Degree](#) can also help connect patients to needed resources.¹⁰⁷⁸⁻¹⁰⁸⁰ Follow-up may need to be more frequent for patients who are at intermediate or high risk of toxic stress to monitor for signs and symptoms of dysregulated neuro-endocrine-immune-metabolic systems.

This report recognizes that meaningful and supportive conversations between patients and providers are a critical first step to addressing ACEs and toxic stress. This section is intended to bring awareness of existing evidence-based and promising practices available to be deployed in the primary care setting, in addition to community-based interventions and referral options. With advances in

neuroscience, we now know that the brain continues to grow and rewire itself at all ages throughout life. Thus, interventions and acquisition of new skills can be utilized throughout the life course to improve patient outcomes. Overall, providers can use the key strategies for mitigating the toxic stress response along with a trauma-informed approach to further assess and treat children and adults impacted by ACEs.

While this report highlights current science-based interventions for mitigating the toxic stress response, it also recognizes that advances in treatment are necessary to achieve the bold goal of cutting ACEs and toxic stress in half in a generation. Investments in basic science and clinical and translational research are needed to improve diagnostic precision and treatment efficacy for toxic stress and its potential subtypes, and to identify more precise therapeutic targets.

Case Study

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder in childhood and can include symptoms of hyperactivity, inattention, and impulsivity.¹⁰⁵⁵ ADHD and toxic stress can present with similar symptoms, and a diagnosis of ADHD has been associated with higher ACE exposure.¹⁰⁵⁶ Diagnosis of ADHD is based on symptoms as defined in the Diagnostic and Statistical Manual of Mental Health Disorders, fifth edition (DSM-V). Toxic stress is defined by physiologic derangements in the biological stress response and concomitant neuro-endocrine-immune-metabolic and genetic regulatory dysregulation. Therefore, it has yet to be determined whether toxic stress predisposes for ADHD, or whether the ADHD-like symptom profile of toxic stress may represent a separate disease entity. Further research to confirmatively establish diagnostic criteria for toxic stress will aid in answering this question, which may have implications for treatment.

Clinically, the standard treatment for ADHD includes therapy in combination with medications. Psychostimulants such as methylphenidate, amphetamine, and atomoxetine, which stimulate catecholamine signaling, are the best known and most widely used medications for ADHD treatment.^{1055,1057} For many patients with ADHD (and without toxic stress), deficits in the neurotransmitters norepinephrine and dopamine contribute to symptoms, and this treatment effectively increases attention, working memory, and performance. However, for children experiencing toxic stress who have prolonged activation of the stress response system, this course of treatment may not be the most effective first-line intervention because catecholamine signaling is already too high. Treatment with an α 2-adrenergic receptor-activating drug such as guanfacine, which opposes the actions of catecholamine signaling, mitigates effects of toxic stress on attention by directly improving prefrontal cortex functions like executive function and attention.^{1018,1058-1060} Importantly, pharmacological treatment for ADHD is most effective when applied in conjunction with other interventions targeted at reducing environmental risk factors, addressing underlying toxic stress physiology by utilizing stress-buffering strategies, and behavioral therapy.

Case Study

Asthma

As discussed in the **Biological Embedding of Toxic Stress** section in Part I, asthma is a chronic, relapsing inflammatory disease that is more prevalent in people with high ACEs.^{229,1061} It is characterized by episodic shortness of breath, cough, wheezing, and/or chest tightness. Toxic stress-related inflammation and airway constriction can mediate this increased disease burden. Children experiencing adversity are more likely to be exposed to factors associated with increased incidence and severity of asthma, such as indoor air pollutants like tobacco smoke and living in communities near highways.^{1062,1063,1064} Prolonged activation of the stress response is also directly associated with increased risk of asthma. Children with clinical biomarkers of toxic stress physiology were found to have 5.5-fold reduction in glucocorticoid receptor mRNA and 9.5-fold lower β 2-adrenergic receptor mRNA levels in one study.²³¹ Such biological changes decrease the sensitivity of the lung to the actions of glucocorticoids like prednisone and bronchodilators like albuterol, the two standard elements of treatment for acute asthma exacerbations. Thus, these “standard” treatments may be less effective for children with toxic stress and asthma.²³⁰

Treatment considerations for children whose asthma may be associated with toxic stress are thus different from children without toxic stress. Shared decision-making, the desired norm in all healthcare contexts, also improves self-management in people with asthma and leads to improved outcomes.¹⁰⁶⁵ Identifying and removing or mitigating sources of stress may improve responses to standard treatments. For example, a study of 150 children (9-17 years) with physician-diagnosed asthma found that parental perspective-taking was associated with children having smaller inflammatory responses to stimulation by non-specific, asthma-specific, and viral analogue ligands, and a greater sensitivity to the anti-inflammatory effects of glucocorticoids.⁶⁷⁰ Additional steps to mitigate underlying toxic stress, such as the key intervention strategies described above, may help normalize physiology, thus increasing efficacy of standard treatments. These findings are reflected in draft consensus statements on ACEs, toxic stress, and asthma by the National Committee on Asthma and Toxic Stress, which recommends social support, exercise, mindfulness practices (meditation, yoga, tai chi, hypnosis), exposure to nature, and nutritional approaches, in addition to standard asthma management practices.¹⁰⁶⁶⁻¹⁰⁷⁷