

August 9, 2023

# Toxic Stress and Women's Health: Impacts and Opportunities

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# ADVERSE CHILDHOOD EXPERIENCES (ACES)

## Abuse



Physical



Emotional



Sexual

## Neglect



Physical



Emotional

## Household Challenges



Mental  
Illness



Intimate  
Partner  
Violence



Parental  
Separation  
or Divorce



Incarceration



Substance  
Misuse or  
Dependence

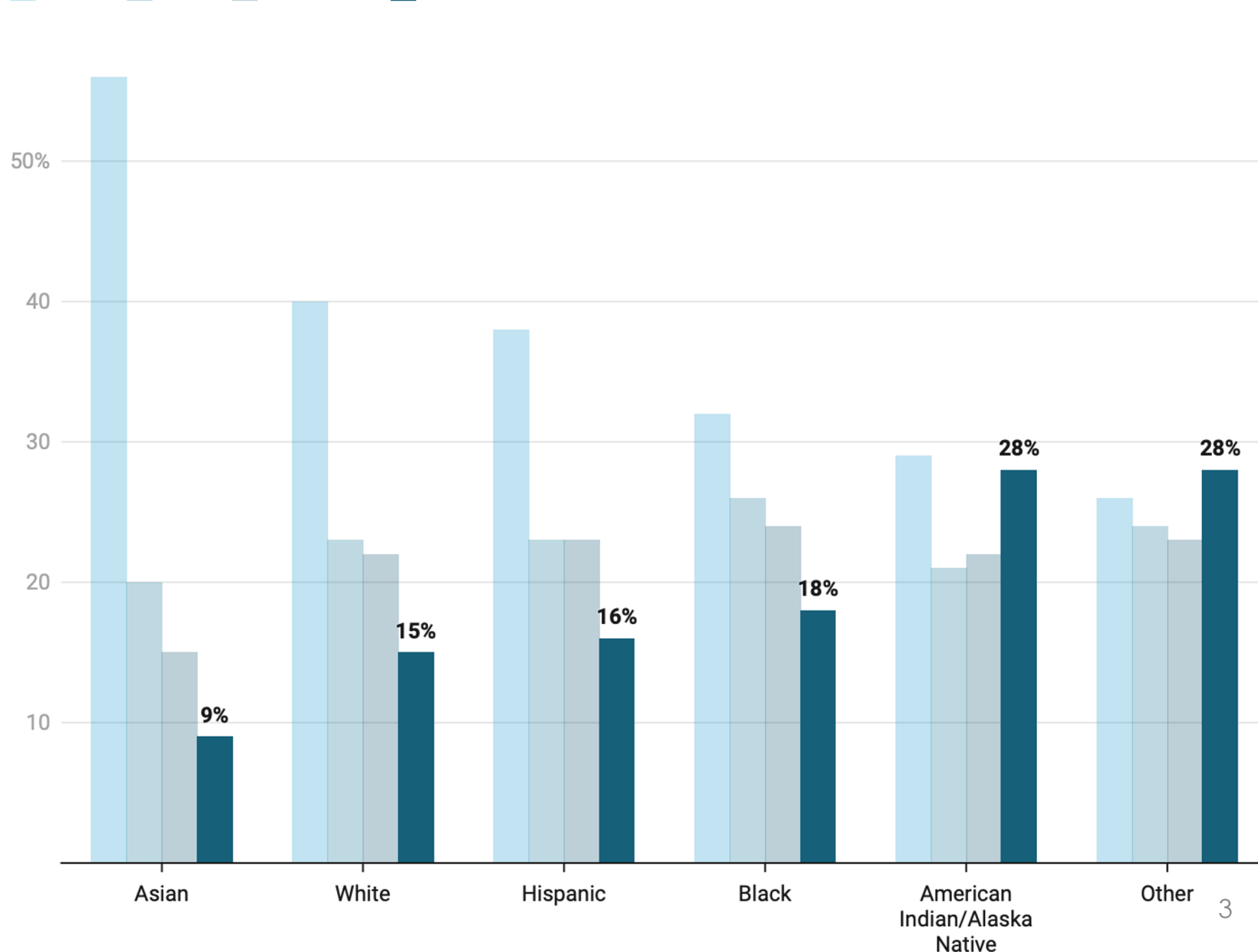
**Almost 2/3 of U.S. adults have experienced ACEs, however exposure is unequally distributed by race and ethnicity**

\*Sociodemographic characteristics of adults in the study population, by adverse childhood experience score\* — Behavioral Risk Factor Surveillance System (BRFSS), 25 states,† 2015–2017; Source: US Department of Health and Human Services/Centers for Disease Control and Prevention MMWR / November 8, 2019 / Vol. 68 / No. 44.

## Exposure to ACEs is unequally distributed by race and ethnicity in the United States

Prevalence of ACEs among U.S. adults, by race and ethnicity, 2015-2017

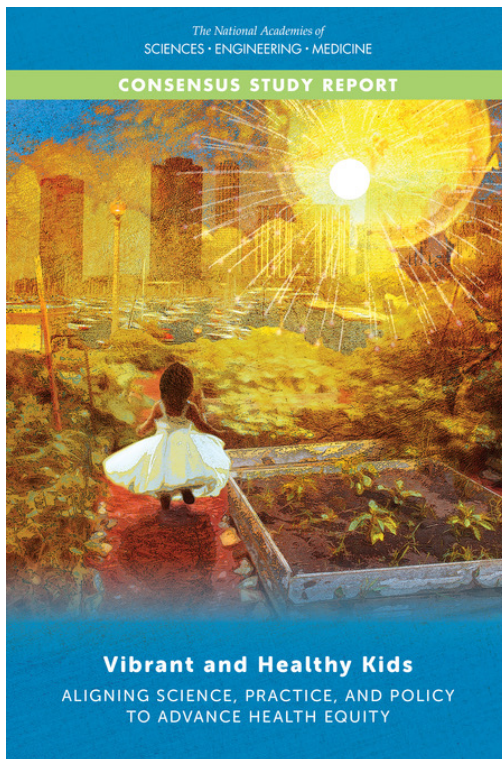
0 ACEs 1 ACE 2 to 3 ACEs Four or more ACEs



# ACES ARE ASSOCIATED WITH INCREASED RISK FOR 9 OF THE 10 LEADING CAUSES OF DEATH IN THE U.S.

Leading Causes of Death in the U.S., 2021		Odds Ratios for $\geq 4$ ACEs (relative to no ACEs)
1	Heart disease	2.1
2	Cancer	2.3
3	COVID-19	Unknown
4	Accidents (unintentional injuries)	2.6
5	Stroke	2.0
6	Chronic lower respiratory disease	3.1
7	Alzheimer's disease or dementia	11.2
8	Diabetes	1.4
9	Chronic liver disease	2.4
10	Kidney disease	1.7

# THE TOXIC STRESS RESPONSE DEFINED



*“prolonged activation of the stress response systems that can disrupt the development of brain architecture and other organ systems, and increase the risk for stress-related disease and cognitive impairment, well into the adult years...”*

THE BIOLOGY OF

# ADVERSITY



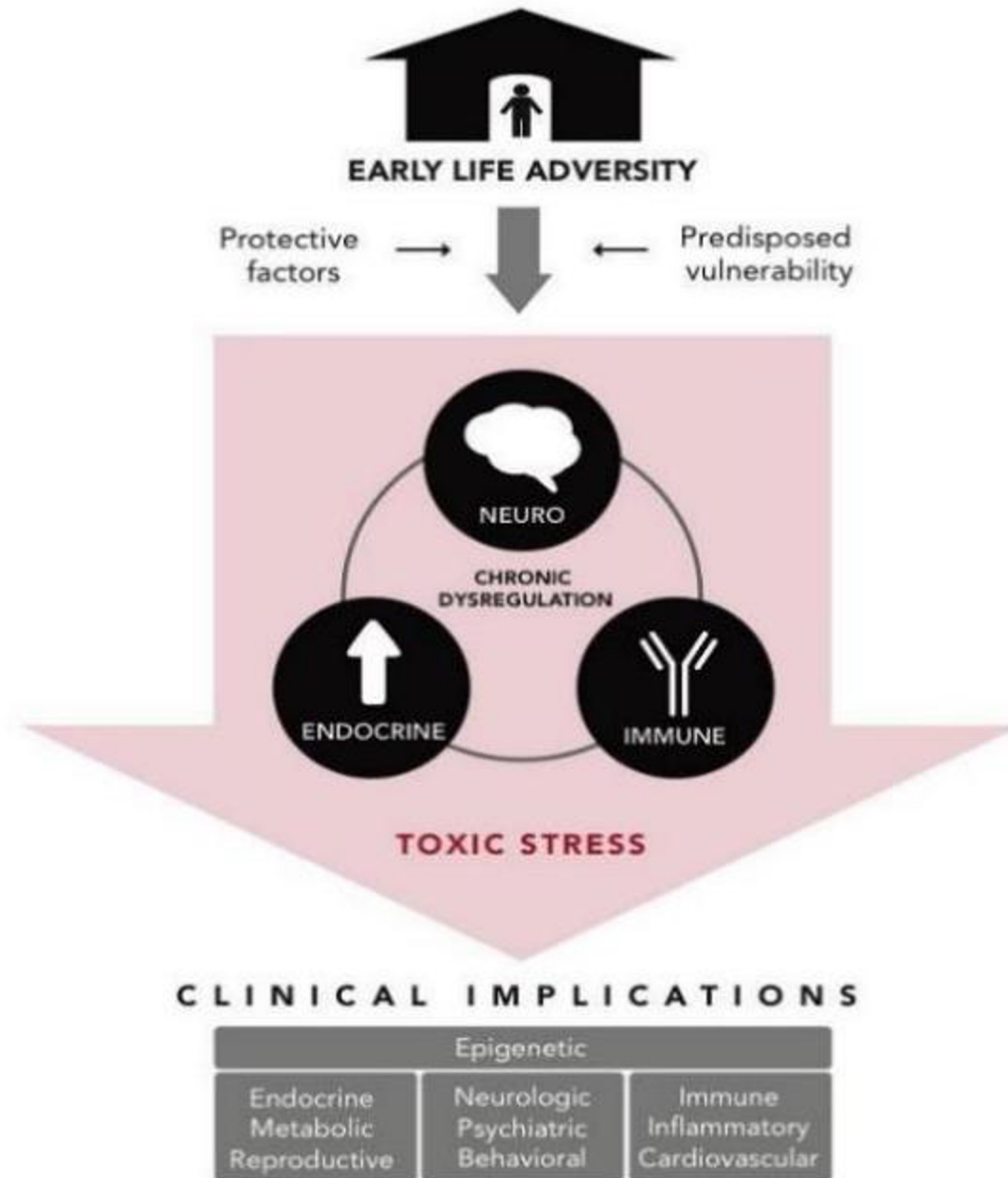










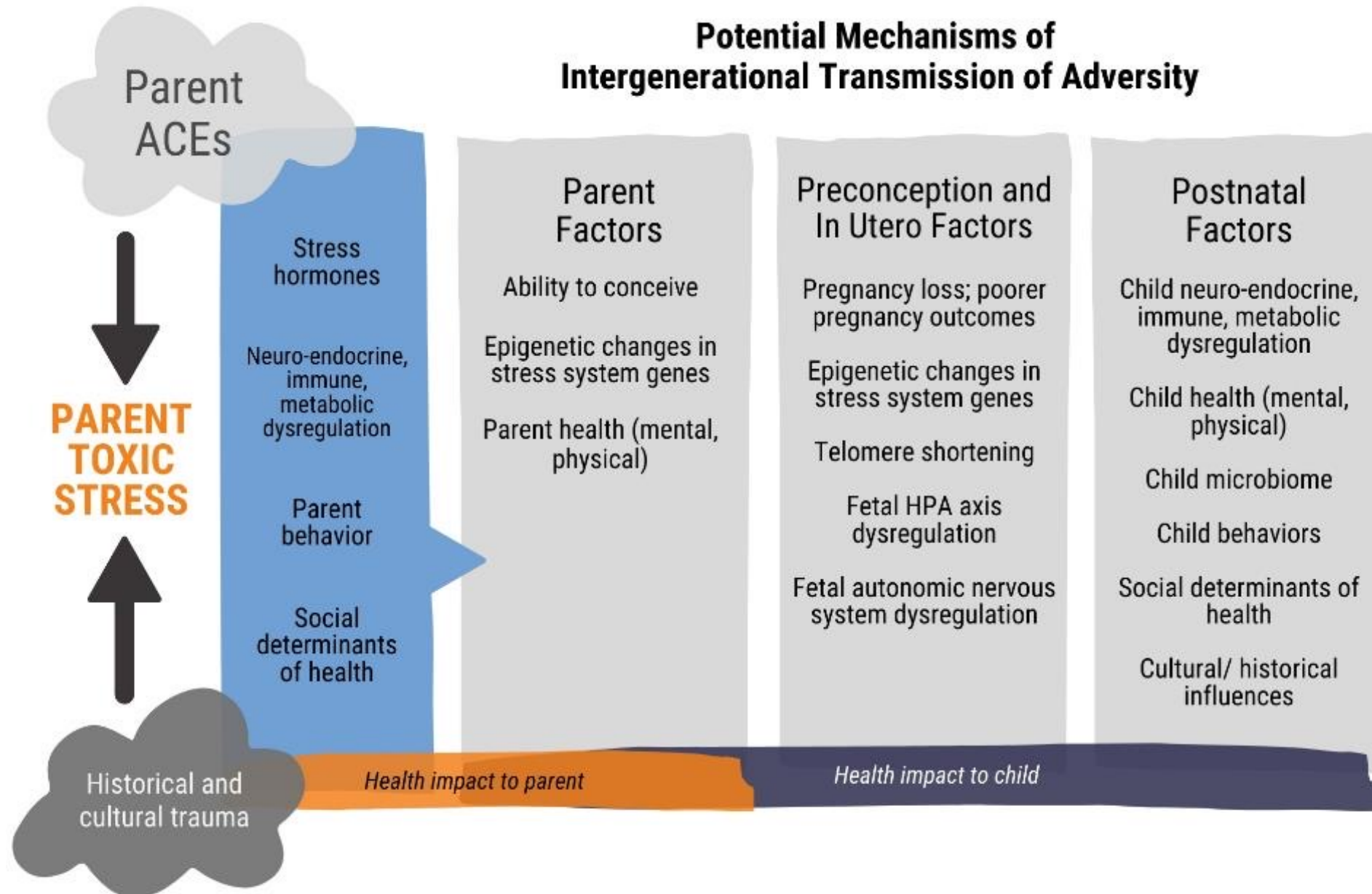


Source: Adapted from Bucci et al, 2016

# Biological systems disrupted by toxic stress

SYSTEM	MECHANISM(S)	HEALTH IMPACT
<b>Neurologic; Neuroendocrine</b>	- Dysregulation of SAM and HPA axes; autonomic imbalance	Difficulty modulating, sustaining, or dampening the stress response; heightened or blunted stress sensitivity
	- Altered reactivity and size of the amygdala	Increased fear responsiveness, impulsivity, and aggression
	- Inhibition of the prefrontal cortex	Impaired executive function, with poorer planning, decision-making, impulse control, and emotion regulation
	- Hippocampal neurotoxicity	Difficulty with learning and memory
	- VTA and reward processing dysregulation	Increased risky behaviors and risk of addiction
<b>Immunologic; Inflammatory</b>	- Increased inflammatory markers, especially Th2 response; inhibition of anti-inflammatory pathways; gut microbiome dysbiosis	Increased risk of infection, auto-immune disorders, cancers, chronic inflammation; cardiometabolic disorders
<b>Endocrine/ Metabolic</b>	- Changes in growth hormone, thyroid hormone, and pubertal hormonal axes	Changes in growth, development, basal metabolism, and pubertal events
	- Changes to leptin, ghrelin, lipid and glucose metabolism, and other metabolic pathways	Increased risk of overweight, obesity, cardiometabolic disorders, and insulin resistance
<b>Epigenetic/ Genetic</b>	- Sustained changes to the way DNA is read and transcribed	Mediates all aspects of the toxic stress response
	- Telomere erosion, altered cell replication, and premature cell death	Increased risk for disease, cancer, and early mortality

## Potential Mechanisms of Intergenerational Transmission of Adversity



Source: Bhushan D, Kotz K, McCall J, Wirtz S, Gilgoff R, Dube SR, Powers C, Olson-Morgan J, Galeste M, Patterson K, Harris L, Mills A, Bethell C, Burke Harris N, Office of the California Surgeon General. Roadmap for Resilience: The California Surgeon General's Report on Adverse Childhood Experiences, Toxic Stress, and Health. Office of the California Surgeon General, 2020.

# ACE-ASSOCIATED HEALTH CONDITIONS: MATERNAL HEALTH

Symptom or Health Condition	Odds Ratio
Pregnancy loss	≥ 5 ACE: 1.7 <sup>2</sup>
Low birth weight	≥ 5 ACE: 1.4 <sup>3</sup>
Preterm birth	≥ 5 ACE: 1.5 <sup>3</sup>
Mental health in pregnancy: Prenatal depressive symptoms PTSD Postpartum depression risk	≥ 1 ACE: 1.3 <sup>5</sup> ≥ 3 ACEs: 1.3 <sup>6</sup> ≥ 5 ACEs: 4.2 <sup>7</sup> ≥1 ACE: 1.34 <sup>5</sup>
Substance use in pregnancy: Smoking Alcohol Illicit drugs	≥ 3 ACEs: 2.6 <sup>8</sup> ≥ 3 ACEs: 3.7 <sup>8</sup> ≥ 3 ACEs: 6.1 <sup>8</sup>
Undesired*** pregnancy	≥ 3 ACEs: 2.6 <sup>10</sup>
Risk of adult male with ACEs impregnating a teen****	≥ 5 ACE: 2.6 <sup>1</sup>





# **Toxic Stress is a Health Condition Amenable to Treatment**

# Other risk factors for toxic stress

*A circumstance, exposure, or condition with documented associations with increased likelihood or susceptibility of development of the toxic stress response.*

*In addition to ACEs, **other risk factors for toxic stress include poverty, exposure to discrimination, and exposure to the atrocities of war.***

# Key Finding - An effective response to ACEs and Toxic Stress requires prevention at all levels

- **PRIMARY PREVENTION** efforts target healthy individuals and aim to prevent harmful exposures from ever occurring.
- **SECONDARY PREVENTION** efforts identify individuals who have experienced an exposure and aim to prevent the development of symptoms, disease, or other negative outcomes.
- **TERTIARY PREVENTION** efforts target individuals who have already developed a disease or social outcome, and aim to lessen the severity, progression, or complications associated with that outcome.



# Toxic Stress is Amenable to Treatment

- New opportunities to more precisely interrupt the toxic stress response, break the intergenerational cycle of ACEs and toxic stress, and promote an intergenerational cycle of health.
- Early intervention can improve brain, immune, hormonal, and genetic regulatory control of development.
- Treatment of toxic stress in adults may prevent transmission of neuro-endocrine-immune-metabolic and genetic regulatory disruptions in offspring.

Source: Sources: Chino M, Debruyn L. Building true capacity: Indigenous models for Indigenous communities. American Journal of Public Health 2006; 96(4): 596-9.; Bick J, et al. Effect of early institutionalization and foster care on long-term white matter development: A randomized clinical trial. JAMA Pediatrics 2015; 169(3): 211-9.; Miller GE, et al. A family-oriented psychosocial intervention reduces inflammation in low-SES African American youth. Proceedings of the National Academy of Sciences 2014; 111(31): 11287- 92.



# CLINICAL RESPONSE TO ACES AND TOXIC STRESS

1. Applying principles of **trauma-informed care** including establishing trust, safety, and collaborative decision-making.
2. Supplementing usual care for ACE-Associated Health Conditions by providing **patient education** on toxic stress and offering **strategies to regulate the stress response** (using evidence-based strategies for toxic stress regulation).
3. Validating existing **strengths and protective factors**.
4. **Referrals** to patient resources or interventions, such as educational materials, social work, school agencies, care coordination or patient navigation, community health workers.
5. **Follow-up** as necessary, using the presenting ACE-Associated Health Condition(s) as indicators of clinical progress.

# ACE-Associated Health Conditions: Adults

Symptom or Health Condition	Odds Ratio (excluding outliers)
Cardiovascular disease <sup>21</sup> (CAD, MI, ischemic heart disease)	2.1
Tachycardia <sup>27</sup>	≥ 1 ACE: 1.4
Stroke <sup>20</sup>	2.0
Chronic obstructive pulmonary disease (emphysema, bronchitis) <sup>21</sup>	3.1
Asthma <sup>43</sup>	2.2
Diabetes <sup>21</sup>	1.4
Obesity <sup>20</sup>	2.1
Hepatitis or jaundice <sup>1</sup>	2.4
Cancer, any <sup>21</sup>	2.3
Arthritis <sup>22,7</sup> (self-reported)	3 ACEs, HR: 1.5 ≥ 1 ACE: 1.3
Memory impairment <sup>20</sup> (all causes, including dementias)	4.9
Kidney disease <sup>43</sup>	1.7
Headaches <sup>11</sup>	≥ 5 ACEs: 2.1
Chronic pain, any <sup>28</sup> (using trauma z-score)	1.2
Chronic back pain <sup>28</sup> (using trauma z-score)	1.3
Fibromyalgia <sup>27</sup>	≥ 1 ACE: 1.8
Unexplained somatic symptoms, including somatic pain, headaches <sup>28,2</sup>	2.0 - 2.7
Skeletal fracture <sup>1</sup>	1.6 - 2.6 <sup>20</sup>
Physical disability requiring assistive equipment <sup>23</sup>	1.8
Depression <sup>21</sup>	4.7
Suicide attempts <sup>21</sup>	37.5
Suicidal ideation <sup>20</sup>	10.5
Sleep disturbance <sup>20</sup>	1.6
Anxiety <sup>21</sup>	3.7
Panic and anxiety <sup>20</sup>	6.8
Post-traumatic stress disorder <sup>27</sup>	4.5
Illicit drug use <sup>21</sup> (any)	5.2
Injected drug, crack cocaine, or heroin use <sup>21</sup>	10.2
Alcohol use <sup>21</sup>	6.9
Cigarettes or e-cigarettes use <sup>25</sup>	6.1
Cannabis use <sup>25</sup>	11.0
Teen pregnancy <sup>21</sup>	4.2
Sexually transmitted infections, lifetime <sup>21</sup>	5.9
Violence victimization <sup>21</sup> (intimate partner violence, sexual assault)	7.5
Violence perpetration <sup>21</sup>	8.1

# S T R E S S   R E S P O N S E

## POSITIVE

Physiological response to mild or moderate stressor

Brief activation of stress response elevates heart rate, blood pressure, and hormonal levels

Homeostasis recovers quickly through body's natural coping mechanisms

*Tough test at school, playoff game*

## TOLERABLE

Adaptive response to time-limited stressor

Time-limited activation of stress response results in short-term systemic changes

Homeostasis recovers through buffering effect of caring adult or other interventions

*Immigration, natural disaster*

## TOXIC

Maladaptive response to intense and sustained stressor

Prolonged activation of stress response in children disrupts brain architecture and increases risk of health disorders

Prolonged allostasis establishes a chronic stress response

*Abuse, neglect, household dysfunction*

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

# Buffering the Toxic Stress Response



**Neurologic/Neuroendocrine:** MRI studies found that institutionalized children randomized to **high-quality nurturant caregiving** showed normalization of the developmental trajectory of white matter structures. **Responsive caregiving** also improves cortisol reactivity in children. **Time in nature** reduces sympathetic nervous system activity and increases parasympathetic activity.



**Immunologic:** **Meditation** was associated with decreased IFN- $\gamma$  and NK cell production of IL-10 and with increased T cell production of IL-4 (anti-inflammatory). **Healthy sleep** reduces infection risk and improves vaccination response, increasing NK cell activity, IL-6, and TNF-alpha levels. **Moderate exercise** decreases infection risk.



**Endocrine/Metabolic:** **Oxytocin** inhibits the stress response, enhances bonding, protects against stress-induced cell death, has anti-inflammatory effects, enhances metabolic homeostasis, and protects vascular endothelium. **Social support** buffers stress-related cardiovascular reactivity and decreases catecholamine levels. The **Mediterranean diet** reduces inflammation and risk for depression, cardiovascular disease, diabetes, and mortality.



**Epigenetic:** Meany and colleagues found that **nurturant caregiving** was associated with epigenetic changes that led to greater stress tolerance, more normal functioning of the stress response, and improved cognitive performance.

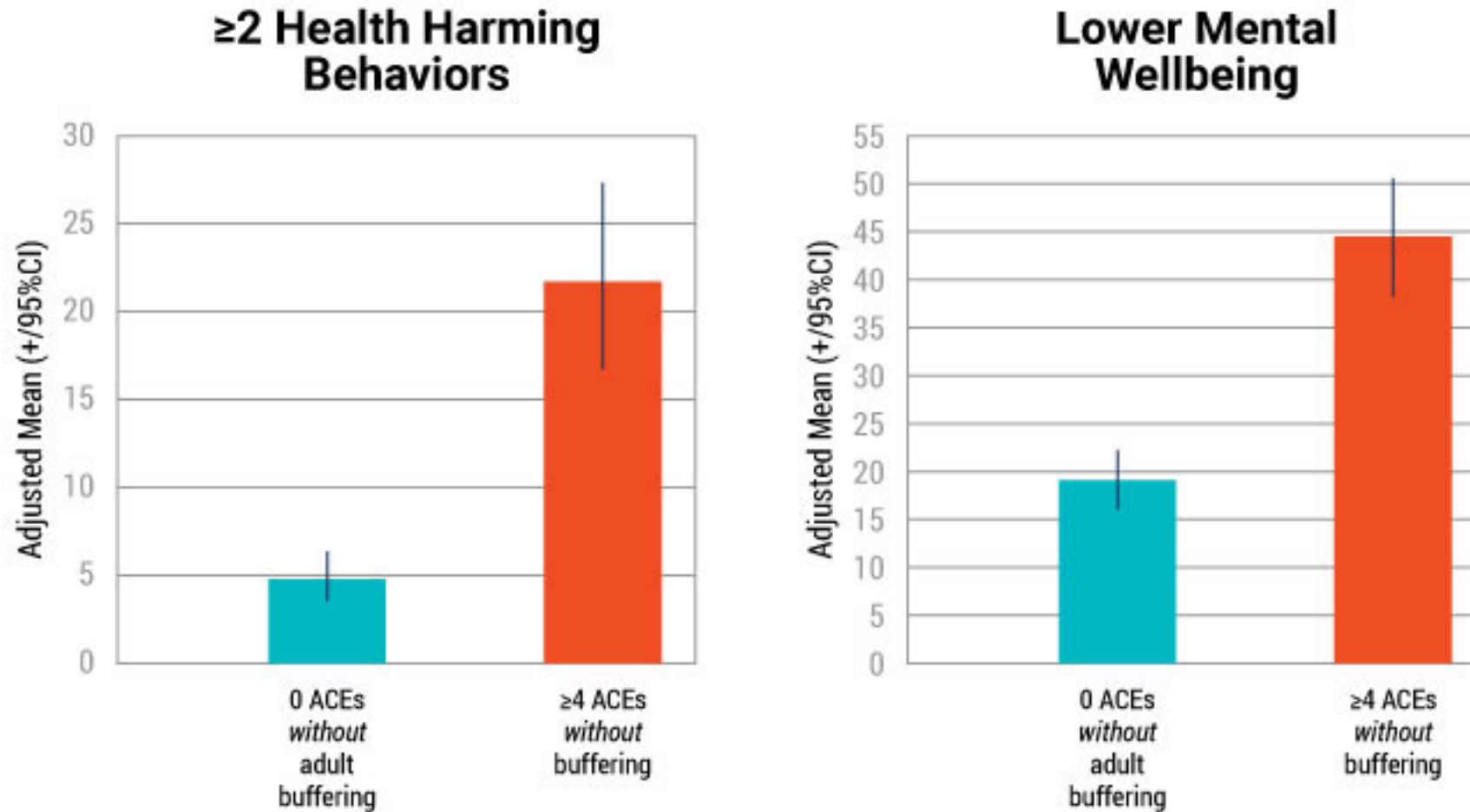


# Evidenced-Based Buffering Interventions



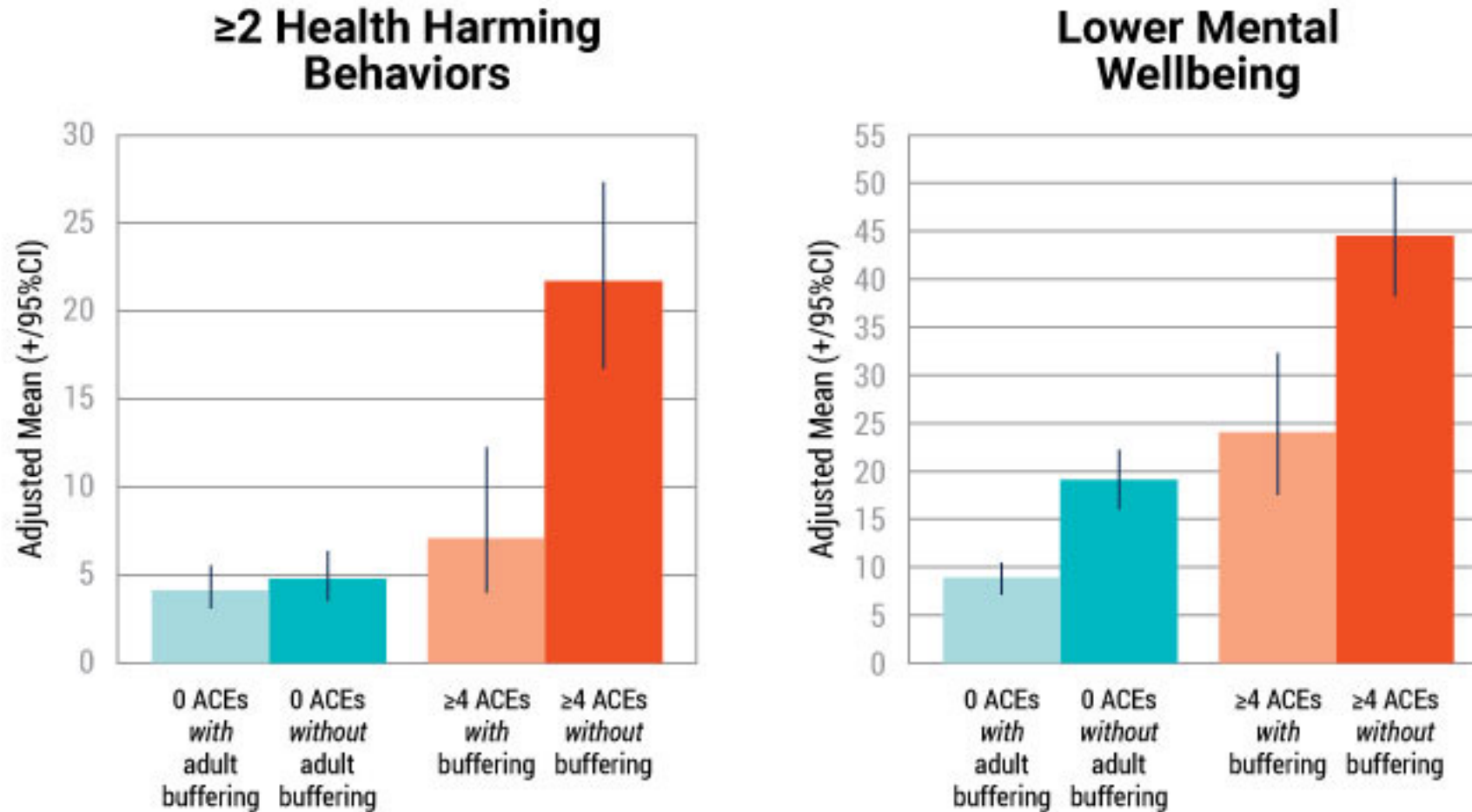
Source: Adapted from Burke Harris, Nadine. *The Deepest Well: Healing the Long-Term Effects of Childhood Adversity*. Boston: Houghton Mifflin Harcourt, 2018.

# IMPACT OF ACES



Source: Mark A. Bellis et al., "Does Continuous Trusted Adult Support in Childhood Impart Life-Course Resilience Against Adverse Childhood Experiences - A Retrospective Study on Adult Health-Harming Behaviours and Mental Well-Being," BMC Psychiatry 17, no. 1 (December 2017), <https://doi.org/10.1186/s12888-017-1260-z>.

# IMPROVED HEALTH OUTCOMES



Source: Mark A. Bellis et al., "Does Continuous Trusted Adult Support in Childhood Impart Life-Course Resilience Against Adverse Childhood Experiences - A Retrospective Study on Adult Health-Harming Behaviours and Mental Well-Being," BMC Psychiatry 17, no. 1 (December 2017), <https://doi.org/10.1186/s12888-017-1260-z>.

# ADDRESSING TOXIC STRESS



## Prevent/Address ACEs & Other Stressors (External Events and Environment)

- Provide public education about ACEs, other stressors, and toxic stress prevention
- Address current safety and unmet social needs
- Prevent and interrupt ACEs and other risk factors for toxic stress, including racism and discrimination
- Collaborate across sectors: health care, public health, early childhood, education, social services, justice, and others
- Advocate for proactive public policies and reform deleterious ones
- Implement trauma-informed care principles



## Treat Toxic Stress Physiology (Internal Biology)

- Address neurologic, endocrine, immune, metabolic, and genetic disruptions
- Provide patient education about toxic stress and strategies to regulate the stress response: supportive relationships, quality sleep, balanced nutrition, physical activity, mindfulness practices, and mental health
- Train providers on clinical interventions
- Engage researchers to further develop biomarkers and therapeutic interventions



## Improved health


- ✓ Physical
- ✓ Mental
- ✓ Emotional
- ✓ Developmental
- ✓ Cognitive
- ✓ Relational
- ✓ Behavioral



# Strong work is already occurring across sectors

Great need for  
coordination

Work must be rooted  
in the science



# **An Evidence-Based Policy Response to ACEs and Toxic Stress**

# California's Foundational Response:

- **Office of the California Surgeon General (CA-OSG)**
  - Provides a rigorous scientific foundation to guide Cross-Sector Coordination
  - Convened cross-governmental effort – ACE Reduction Leadership Team
- **Evidence-Based Policy-Making**
  - Raising Public Awareness and Strengthening Economic Supports for Families
  - Supporting Parents and Children (Home Visiting Expansion, Trauma informed educator training, Investments in Early Learning and Care)
  - Medicaid and Private Insurer Coverage of ACE Screening for Early Detection
  - Training Primary Care Providers on Evidence-Based Approaches to Screening for ACEs and Treatment of Toxic Stress
  - Treatment eligibility based on **risk of toxic stress**
  - Leveraging Precision Medicine and Stem Cell Research to Advance Toxic Stress Measurement and Discovery of Therapeutic Targets

# Annual Cost of ACEs to California

Select Health  
Conditions

**\$112.5 B**

- Asthma
- Arthritis
- COPD
- Depression
- Cardiovascular disease
- Smoking
- Heavy Drinking
- Obesity

Child Abuse and Neglect:  
Other Sectors

**\$19.3 B**

- Education
- Welfare
- Criminal justice
- Lifetime productivity
- Healthcare, early death

Source: Miller TR, Waehrer GM, Oh DL, Purewal Boparai S, Ohlsson Walker S, Silverio Marques S, et al. (2020) Adult health burden and costs in California during 2013 associated with prior adverse childhood experiences. PLoS ONE 15(1): e0228019. <https://doi.org/10.1371/journal.pone.0228019>; Safe & Sound. The economics of child abuse: A study of California: Safe & Sound, 2019.

# California's Key Tools

- **Scientific Framework Supporting Routine Screening**
  - CDC, NASEM and AAP recommend screening for precipitants of toxic stress
- **Statutory Framework Supporting Screening and Provider Training**
  - AB 340 – Trauma Screening Advisory Group to provide recommendations on specific trauma screening tools which could be utilized by Medi-Cal
  - SB428 (ACEs Equity Act) Requires Private Insurers to cover ACE screening
- **Establishing the ACEs Aware initiative (CA-OSG and DHCS)**
  - Almost \$300 million over six fiscal years allocated to support routine ACE screening in primary care through Medi-Cal
    - Train healthcare providers on how to screen for ACEs and treat toxic stress
    - Reimburse providers for conducting ACE screening of children and adults in Medi-Cal
    - Build capacity for coordinated clinical and community response

# State-Level Cross-Sector Response in Practice:

## “ACEs Aware” initiative



### Healthcare Sector

- First-in-the nation initiative - most comprehensive approach for enacting large-scale screening and intervention for toxic stress
- Trained almost 30K healthcare providers since January 2020
- CA ACEs Learning and Quality Improvement Collaborative (CALQIC), - qualitative and quantitative data on best practices in screening and response from 53 clinics in seven state regions over 18 months.

### Cross-Sector Integration in progress

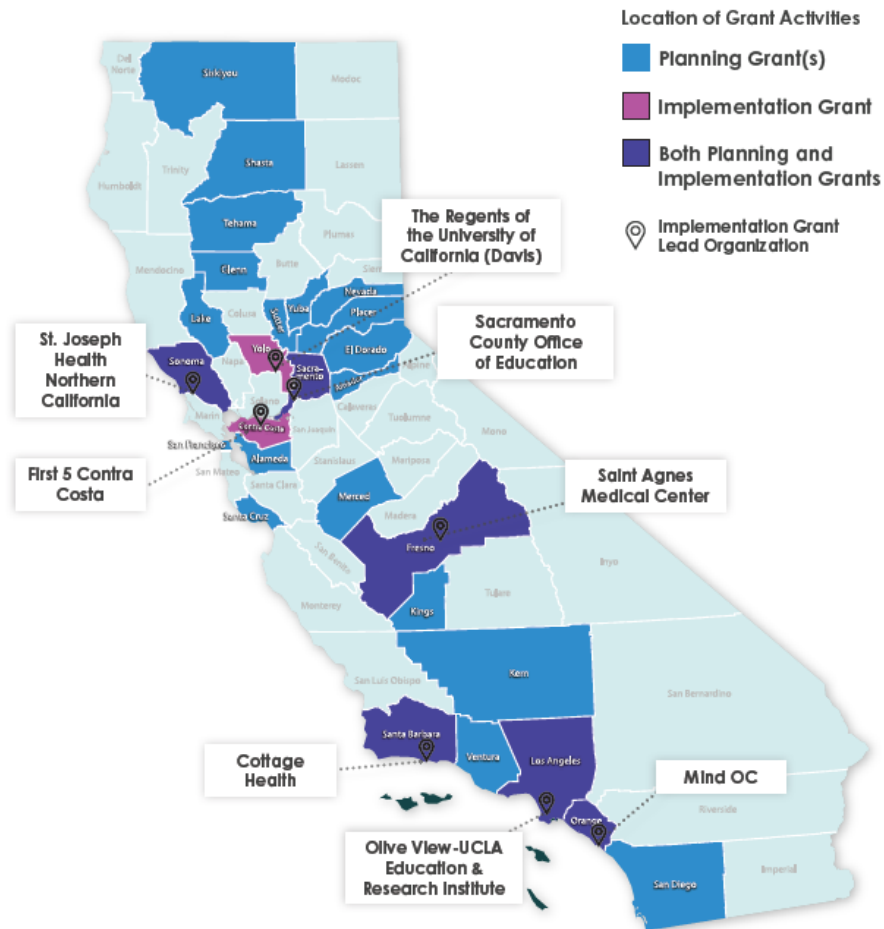
- Trauma Informed Primary Care committee – ACEs Aware advisors
- Network of Care Roadmap
  - Brings alignment to share language, roles, accountability, metrics
  - Local referral systems for cross-sector providers
- Healthcare Provider Directory allows cross-sector responses to refer families in need to ACEs Aware healthcare provider
- >\$50M in community grants to support integration between clinicians and community partners to treat toxic stress





# GROWING NETWORKS OF CARE IN COMMUNITIES

## Trauma Informed Network of Care Grant Awards



- A Network of Care is a group of **interdisciplinary** health, education, and human service professionals, community members, and organizations;
- Supports families by providing access to **evidence-based “buffering” resources** and supports; and
- Helps to **prevent, treat, and heal** the harmful consequences of toxic stress.

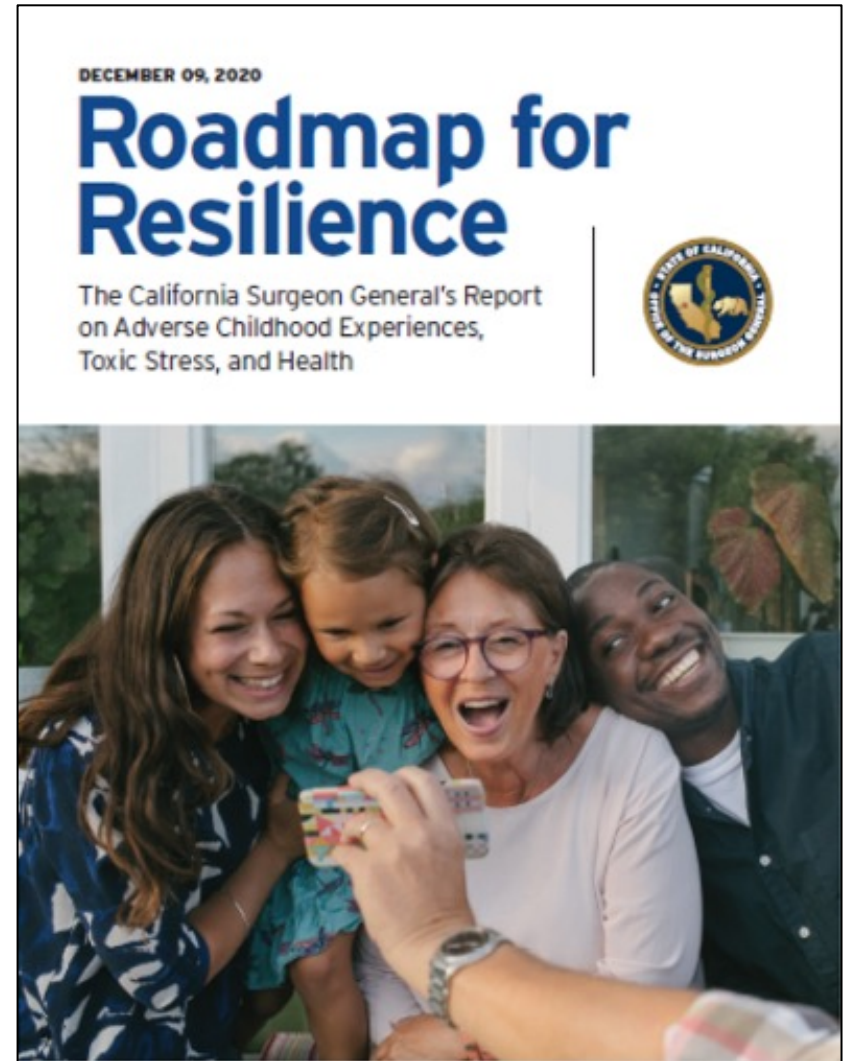
# Further Research is Necessary

Next steps for the movement include advancing a robust toxic stress research agenda. Key objectives should include:

1. Development of clinically relevant **biomarkers** to help more precisely diagnose, classify, and assess treatment efficacy for toxic stress in clinical settings.
2. Guidelines for **clinical management** of ACE-Associated Health Conditions (AAHC's) in the setting of toxic stress.
3. Identification of **therapeutic targets** for regulating the toxic stress response.
4. Elucidation of the complex interactions of how **individual differences** in underlying biological susceptibility or exposures (including timing, severity, duration and developmental interactions) might affect clinical presentation or inform individualized treatment strategies.
5. **Longitudinal studies** are needed to better understand the specific and longer-term impacts of clinical interventions that target the toxic stress response.

# ACES + TOXIC STRESS RESOURCES

- ✓ Free online ACEs Aware Training at [ACESAware.org/training](https://www.acesaware.org/training)
- ✓ Case Studies, Organizational Toolkits & Clinical Resources at <https://www.acesaware.org/resources/>
- ✓ CA Surgeon General's Roadmap for Resilience at [osq.ca.gov/sq-report](https://osq.ca.gov/sq-report)
  - 12 briefs summarizing key themes, including Prevention Strategies in [Health](#), [Education](#), [Social Services](#) and [Justice](#).



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**THANK YOU!**

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