

February 6, 2024

Charting A Course: An Evidence-Based Approach to Addressing ACEs and Toxic Stress at Scale

Dr. Nadine Burke Harris, MD, MPH, FAAP

ACES & TOXIC STRESS ARE A PUBLIC HEALTH

CRISIS

The background features a solid orange color. Faintly visible in the background are a caduceus (a staff with two snakes entwined around it) and a map of the United States, both rendered in a lighter shade of orange.

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

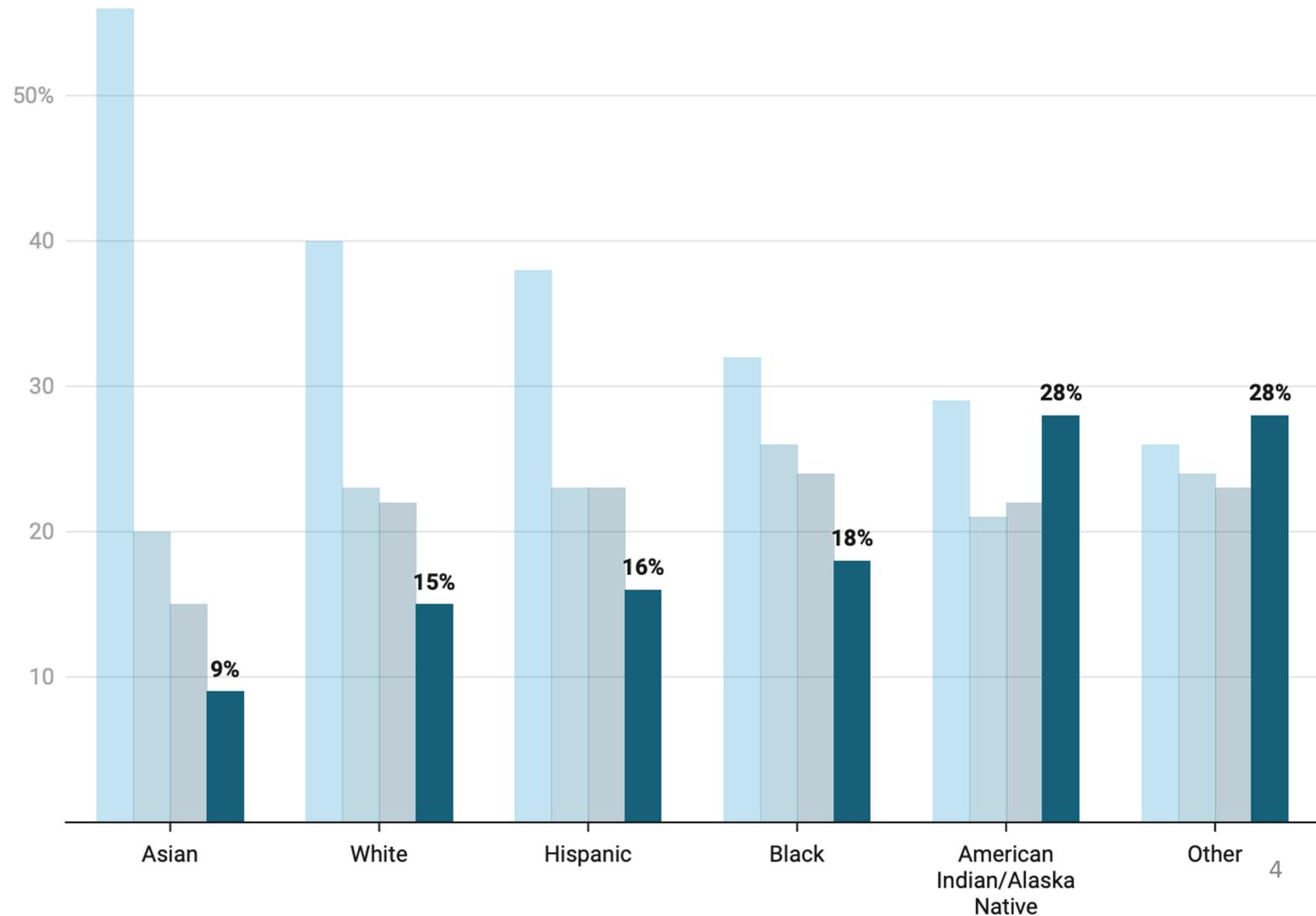
While almost 2/3 of U.S. adults have experienced ACEs, exposure is unequally distributed by race and ethnicity

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.

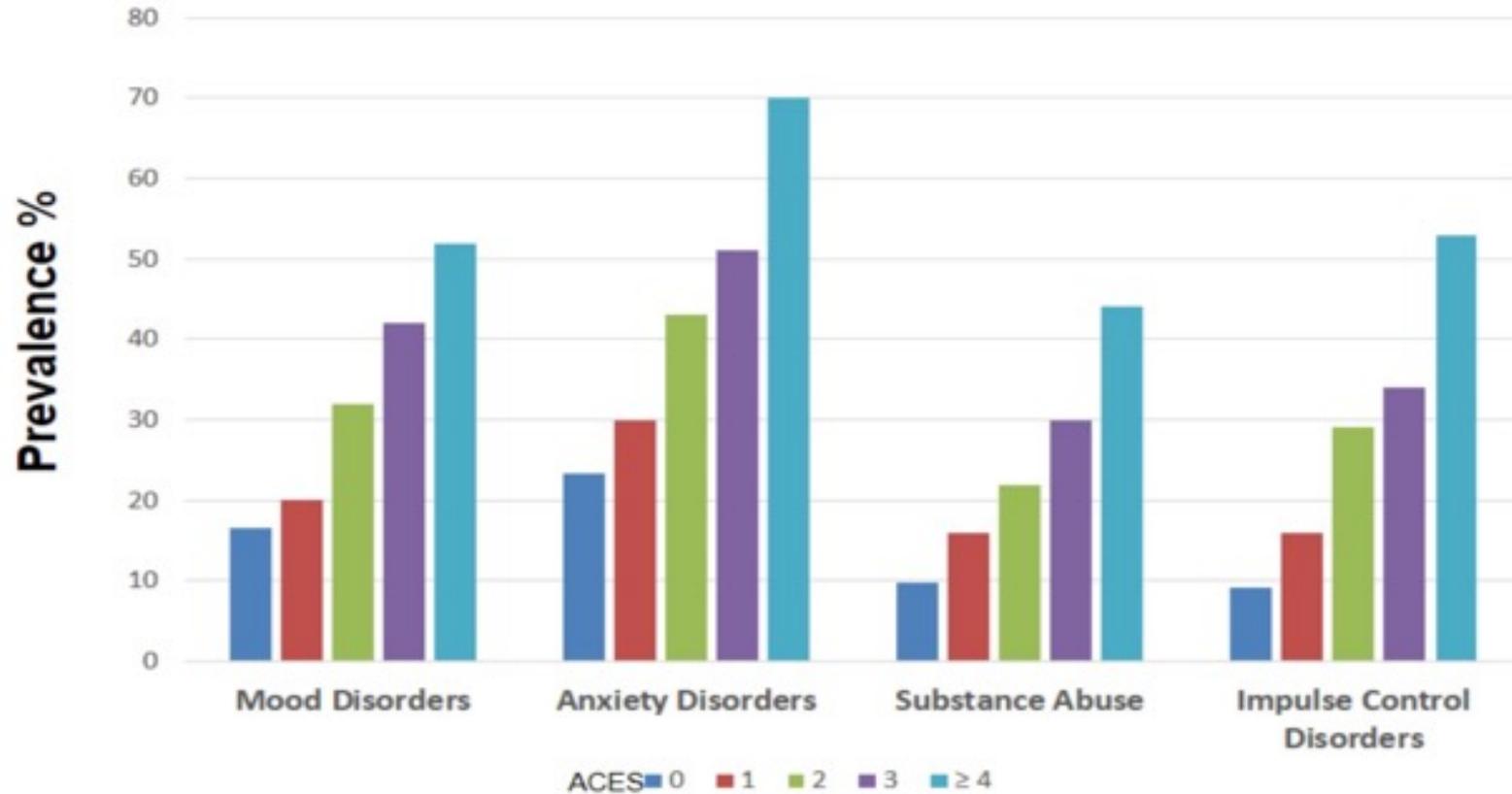
Exposure to ACEs is unequally distributed by race and ethnicity in the United States

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



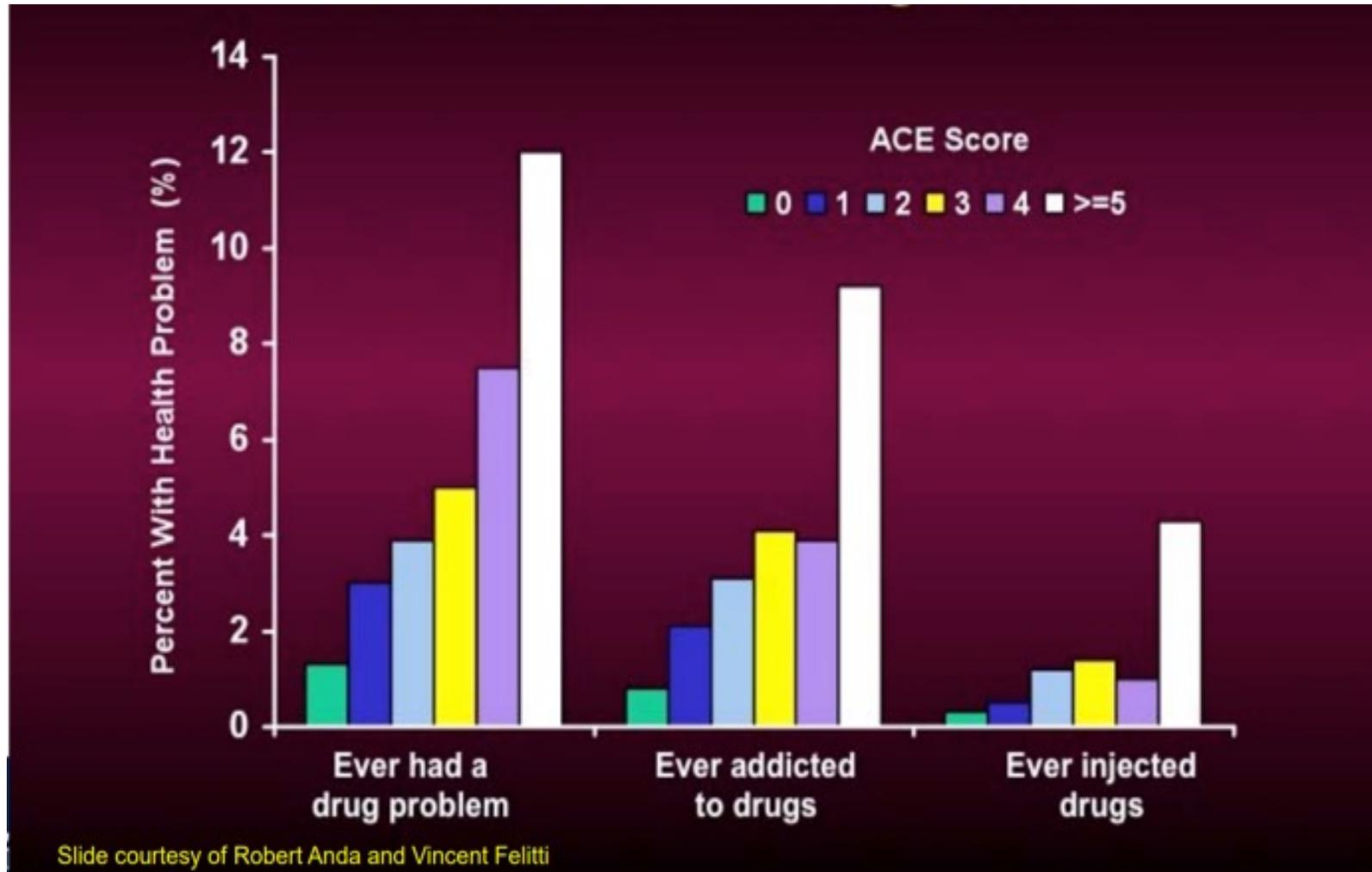
Cumulative ACEs & Mental Health^{1,2}

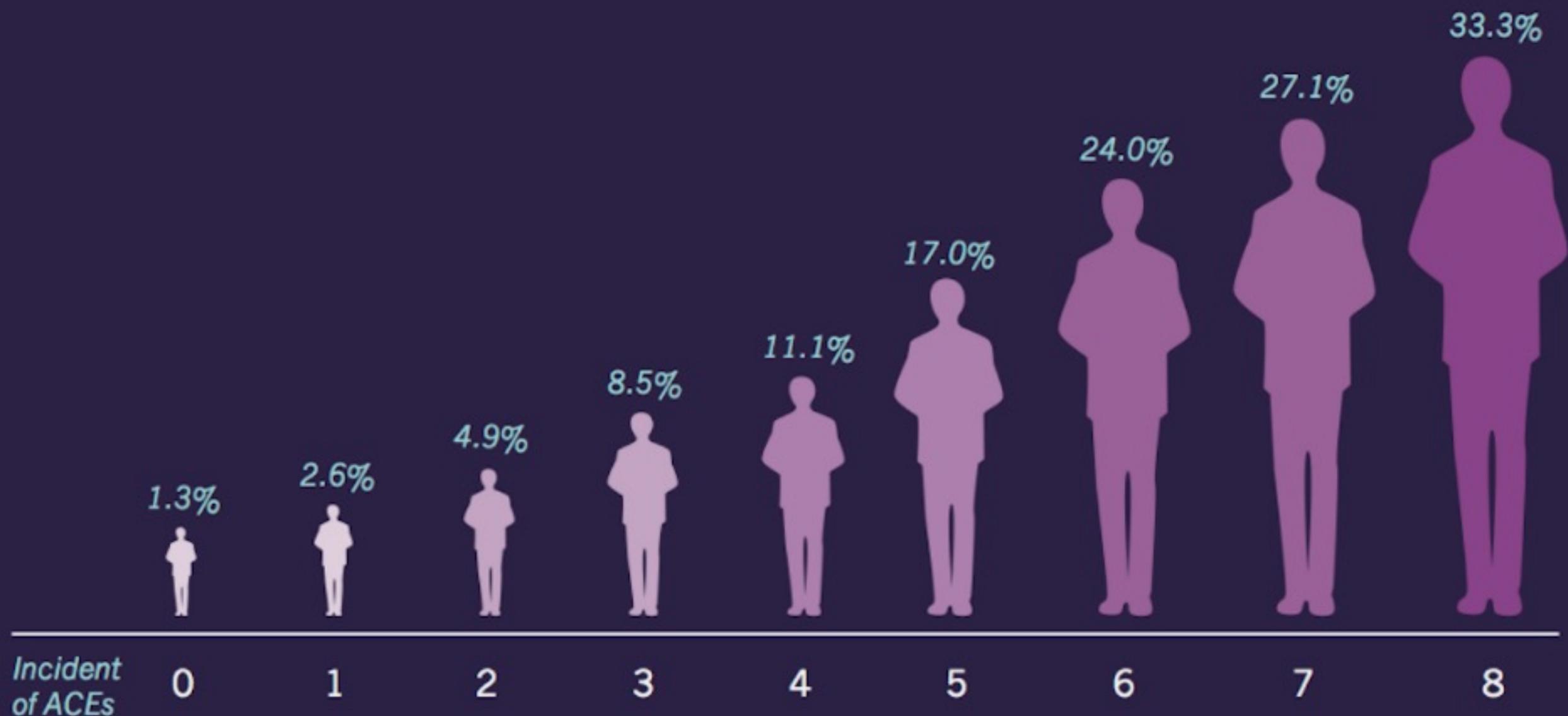


¹Data from the National Comorbidity Survey-Replication Sample (NCS-R).

²Putnam, Harris, Putnam, J Traumatic Stress, 26:435-442, 2013.

ACE Score and Substance Use





ACE Score and Relation to Adult Homelessness

Proportion of Washington residents experiencing adult homelessness (among participants in Washington's Behavioral Risk Factor Surveillance System).³

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 ≥ 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

“Childhood adversity was significantly associated with COVID-19-related hospitalisation and COVID-19-related mortality after adjusting for sociodemographic and health confounders.”

Childhood adversity and COVID-19 outcomes in the UK Biobank

Jamie L Hanson ^{1,2}, Kristen O'Connor,³ Dortehea J Adkins,² Isabella Kahhale^{1,2}

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/jech-2023-221147>).

¹Psychology, University of Pittsburgh, Pittsburgh, PA, USA

²Learning, Research, & Development Center, University of Pittsburgh, Pittsburgh, PA, USA

³Saint Vincent College, Latrobe, Pennsylvania, USA

Correspondence to

Dr Jamie L Hanson, Learning, Research, & Development Center, University of Pittsburgh, Pittsburgh, PA 15260, USA; jamie.hanson@pitt.edu

Received 14 July 2023

Accepted 14 October 2023

Published Online First

1 November 2023

ABSTRACT

Objectives This study aims to investigate the association between childhood adversity and COVID-19-related hospitalisation and COVID-19-related mortality in the UK Biobank.

Design Cohort study.

Setting UK.

Participants 151 200 participants in the UK Biobank cohort who had completed the Childhood Trauma Screen were alive at the start of the COVID-19 pandemic (January 2020) and were still active in the UK Biobank when hospitalisation and mortality data were most recently updated (November 2021).

Main outcome measures COVID-19-related hospitalisation and COVID-19-related mortality.

Results Higher self-reports of childhood adversity were related to greater likelihood of COVID-19-related hospitalisation in all statistical models. In models adjusted for age, ethnicity and sex, childhood adversity was associated with an odds ratio (OR) of 1.227 of hospitalisation (95% CI 1.153 to 1.306, childhood adversity $z=6.49$, $p<0.005$) and an OR of 1.25 of a COVID-19-related death (95% CI 1.11 to 1.424, childhood adversity $z=3.5$, $p<0.005$). Adjustment for potential confounds attenuated these associations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Disparities in COVID-19 outcomes are driven by numerous health and sociodemographic risk factors.
- ⇒ Childhood adversity is associated with lifelong physical health disparities and early mortality.
- ⇒ No known studies to date have examined the association between childhood adversity and COVID-19 mortality and morbidity.

WHAT THIS STUDY ADDS

- ⇒ In the UK Biobank, childhood adversity was significantly associated with COVID-19-related hospitalisation and COVID-19-related mortality.
- ⇒ For both morbidity and mortality, these links were seen in statistical models adjusted for important sociodemographic and physical health confounders.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Modifiable and more proximal psychosocial factors may impact adult health outcomes, including COVID-19-related mortality and

Annual Cost of ACEs in California

Cardiovascular
disease

Smoking

Heavy Drinking

Obesity



Asthma

Arthritis

COPD

Depression

Annual Cost of ACEs in the U.S.



THE BIOLOGY OF

ADVERSITY



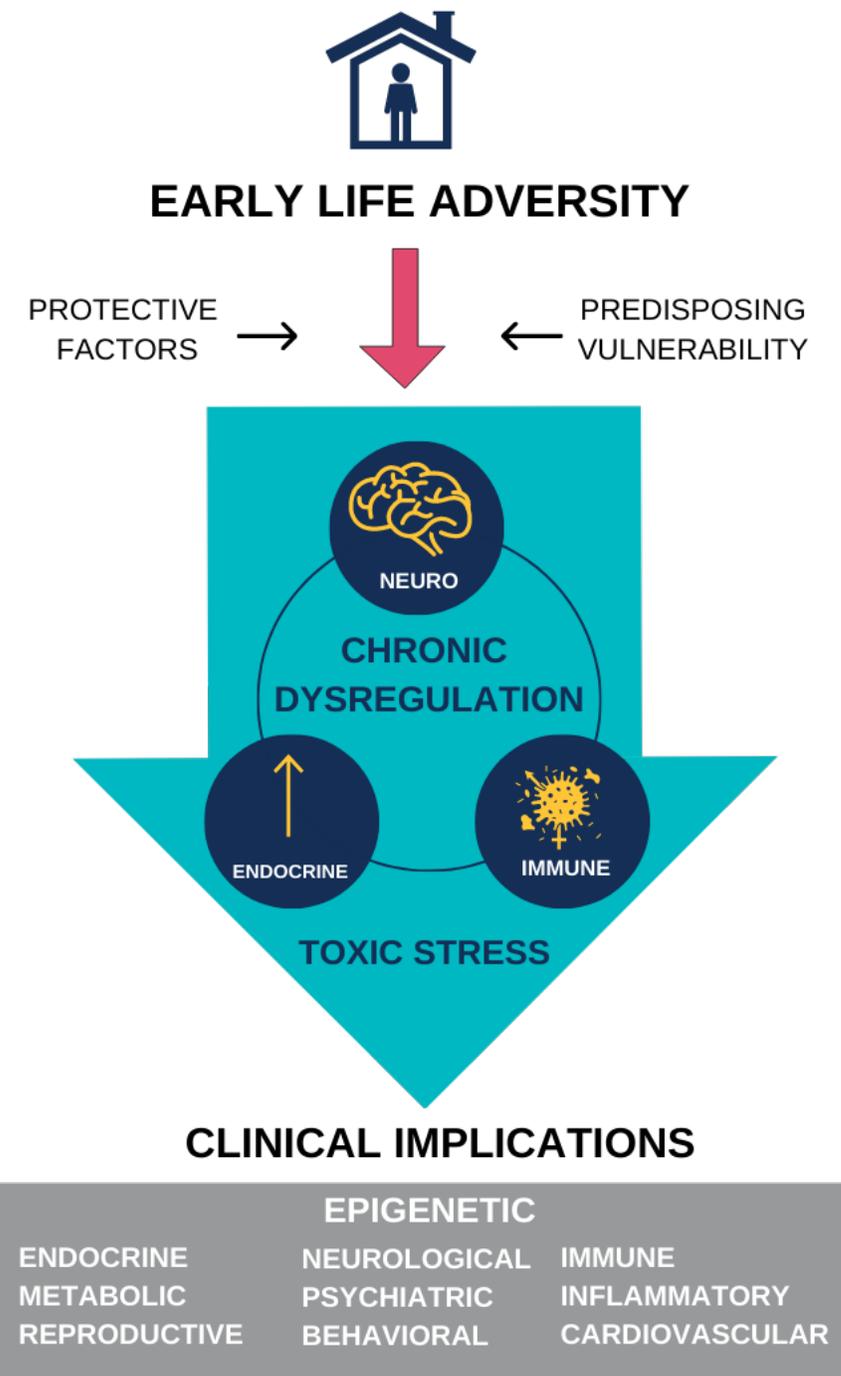




THE TOXIC STRESS RESPONSE

“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...”

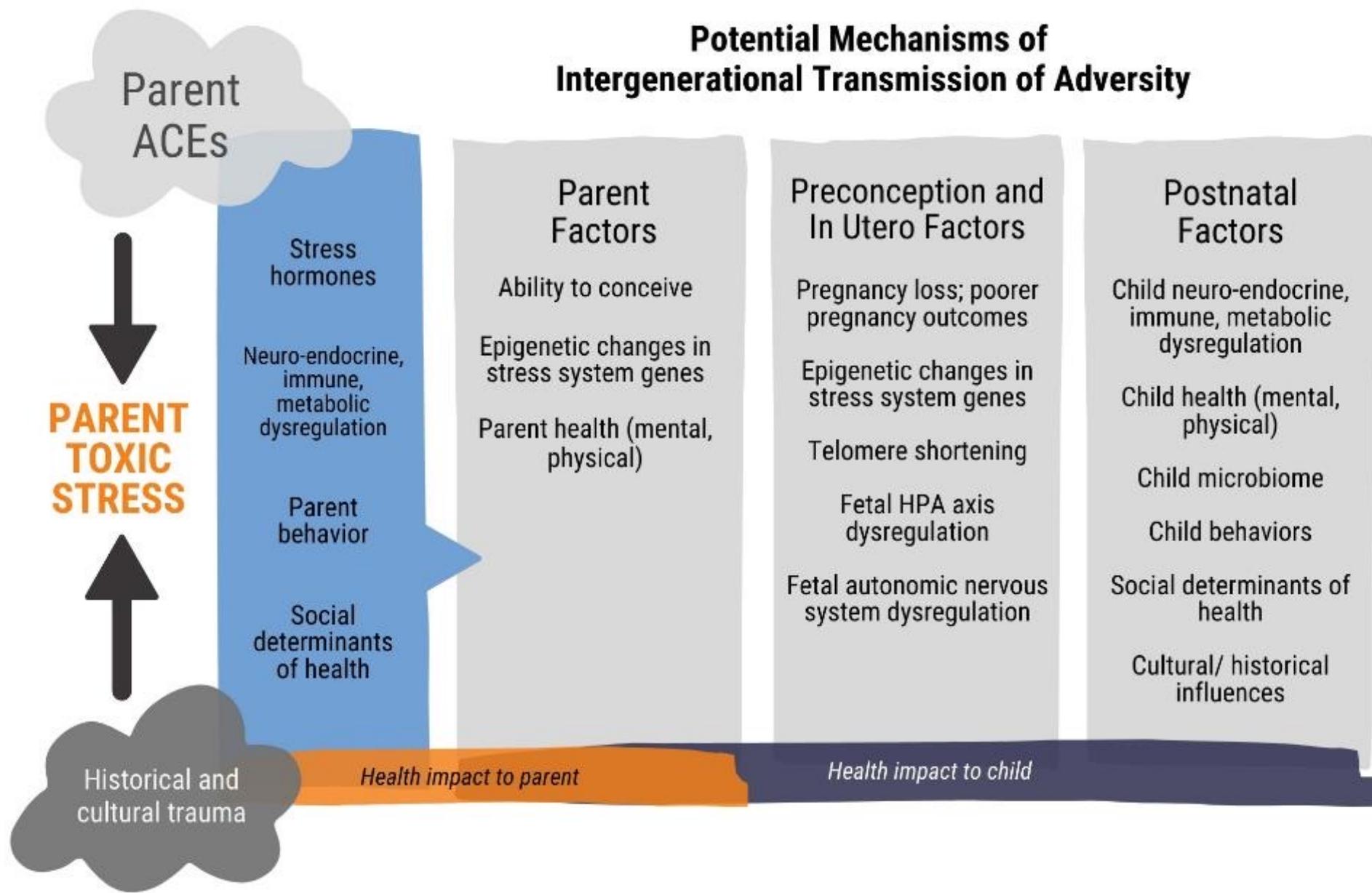
Source: National Academies of Sciences, Engineering, and Medicine. Vibrant and healthy kids: *Aligning science, practice, and policy to advance health equity*. Washington, DC: National Academies Press, 2019.; Nelson CA, Bhutta ZA, Burke Harris N, Danese A, Samara M. Adversity in childhood is linked to mental and physical health throughout life. *BMJ (Clinical Research Edition)* 2020; 371: m3048.



Biological systems disrupted by toxic stress

SYSTEM	MECHANISM(S)	HEALTH IMPACT
Neurologic; Neuroendocrine	- 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
Immunologic; Inflammatory	- 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
Endocrine/ Metabolic	- 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
Epigenetic/ Genetic	- Sustained changes to the way DNA is read and transcribed	Mediates all aspects of the toxic stress response
	- Telomere erosion, altered cell replication, and premature cell death	Increased risk for disease, cancer, and early mortality

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.

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.***

S T R E S S R E S P O N S E

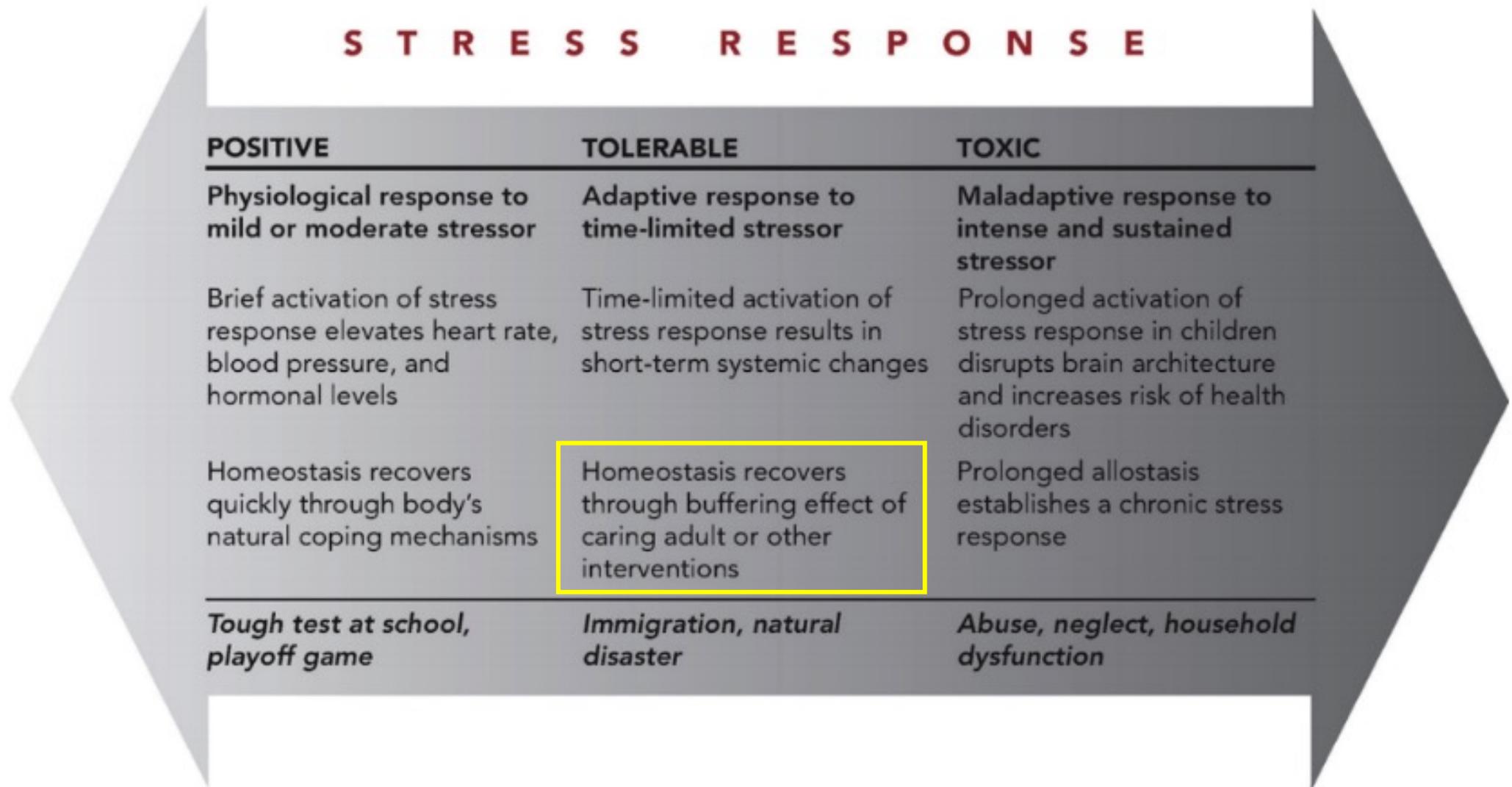


Fig. 2. Spectrum of the stress response: positive, tolerable, and toxic.

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- γ 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.



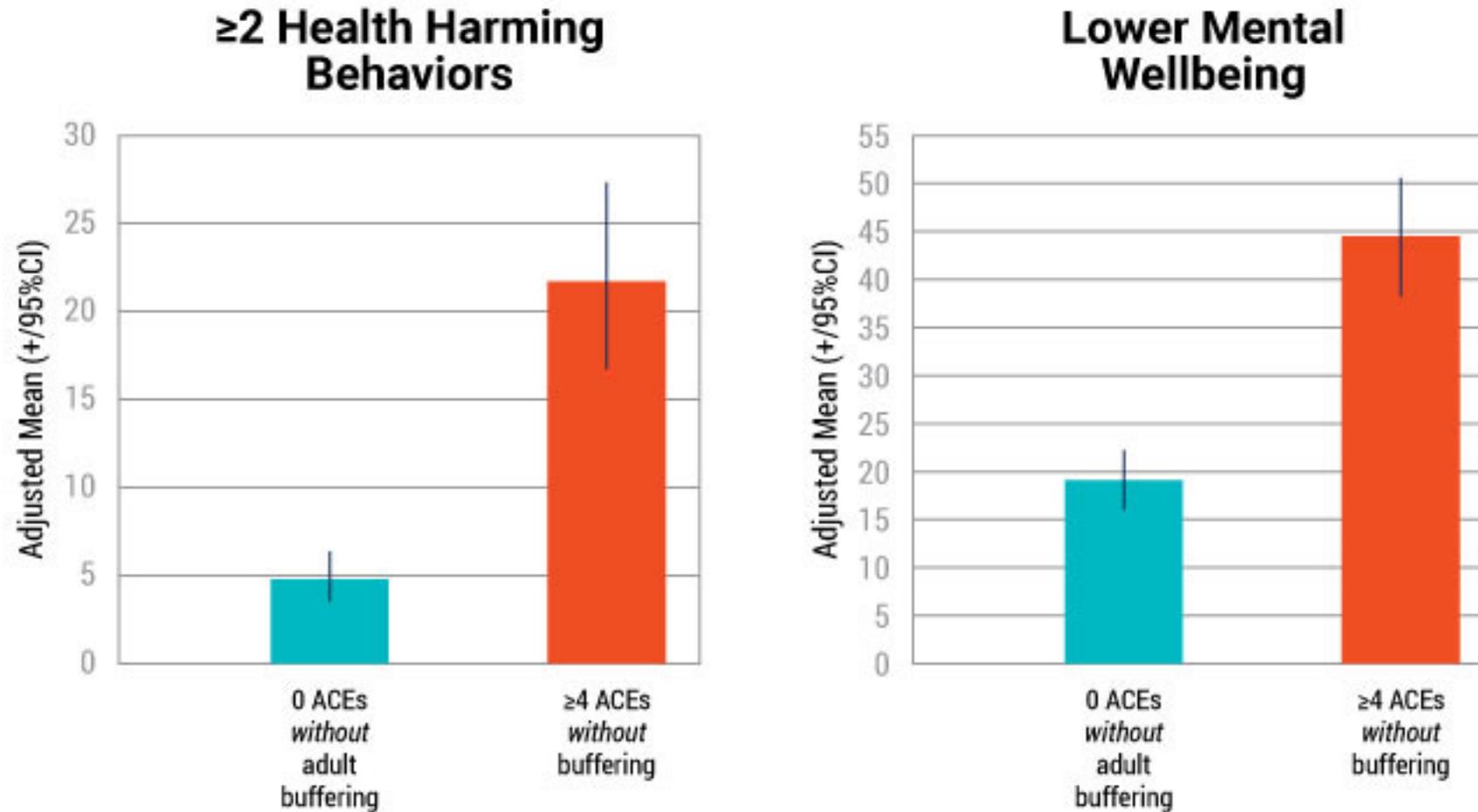
Epigenetic: Meany and colleagues found that **nurturant caregiving** was associated with epigenetic changes that led to greater stress tolerance, more normal functioning of the stress response, and improved cognitive performance.

Evidenced-Based Buffering Interventions



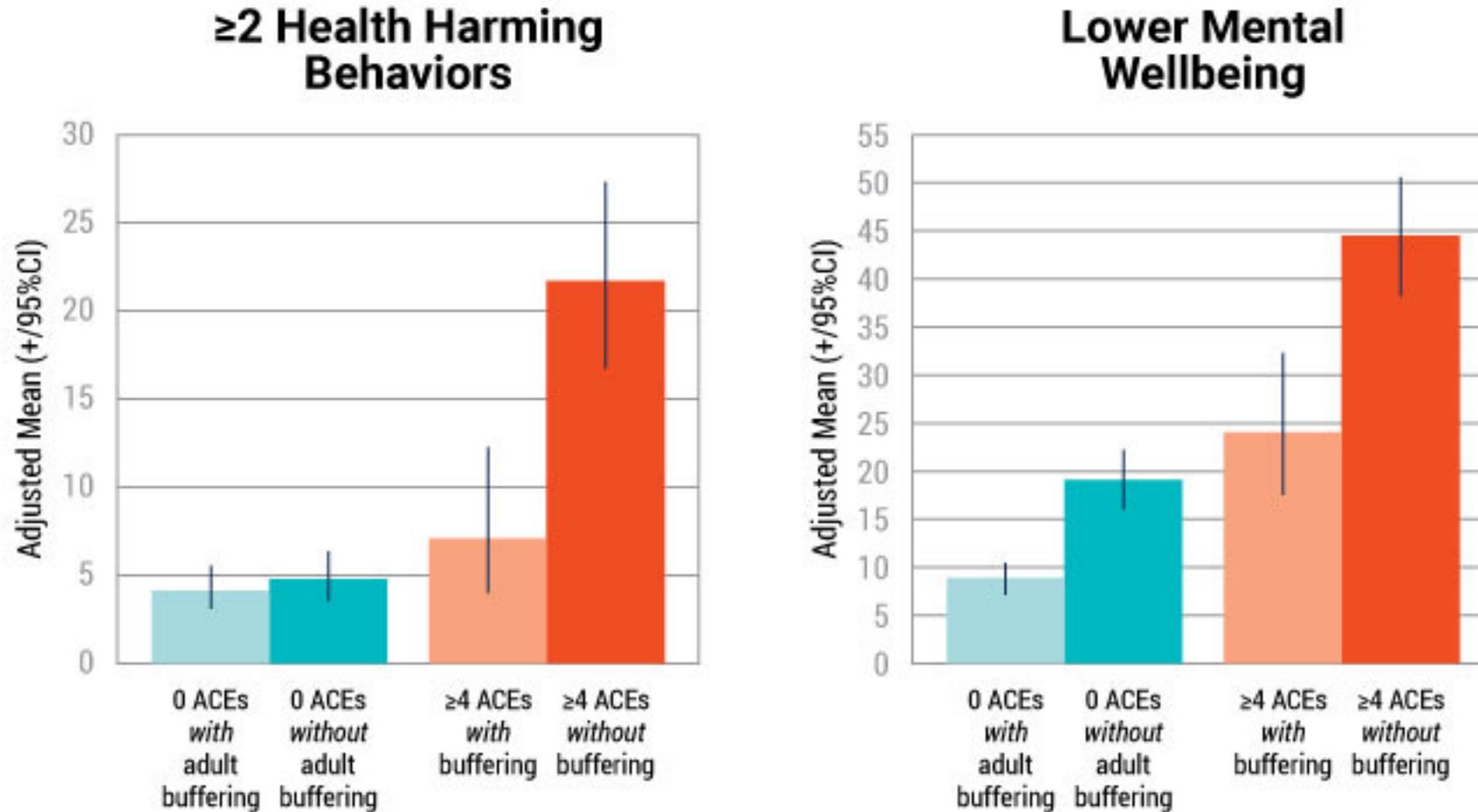
Source: Adapted from Burke Harris, Nadine. *The Deepest Well: Healing the Long-Term Effects of Childhood Adversity*. Boston: Houghton Mifflin Harcourt, 2018.

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>.

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, Debruyne 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;

CA Surgeon General's Report

- Combines perspectives on ACEs and toxic stress from global experts across sectors, specialties and disciplines
- **Toxic Stress is a health condition that is amendable to treatment**
- **Prevention at all levels**
 - An effective response requires prevention at all three levels: primary, secondary, and tertiary. None of these strategies is sufficient alone, and each extends the reach of the others.
- **Cross-Sector Approach**
 - Addressing this public health crisis requires shared understanding of the problem, shared language, clarity of roles, shared metrics, and accountability

DECEMBER 09, 2020

Roadmap for Resilience

The California Surgeon General's Report
on Adverse Childhood Experiences,
Toxic Stress, and Health



NO SINGLE SECTOR OR CATEGORY OF PREVENTION IS SUFFICIENT ALONE

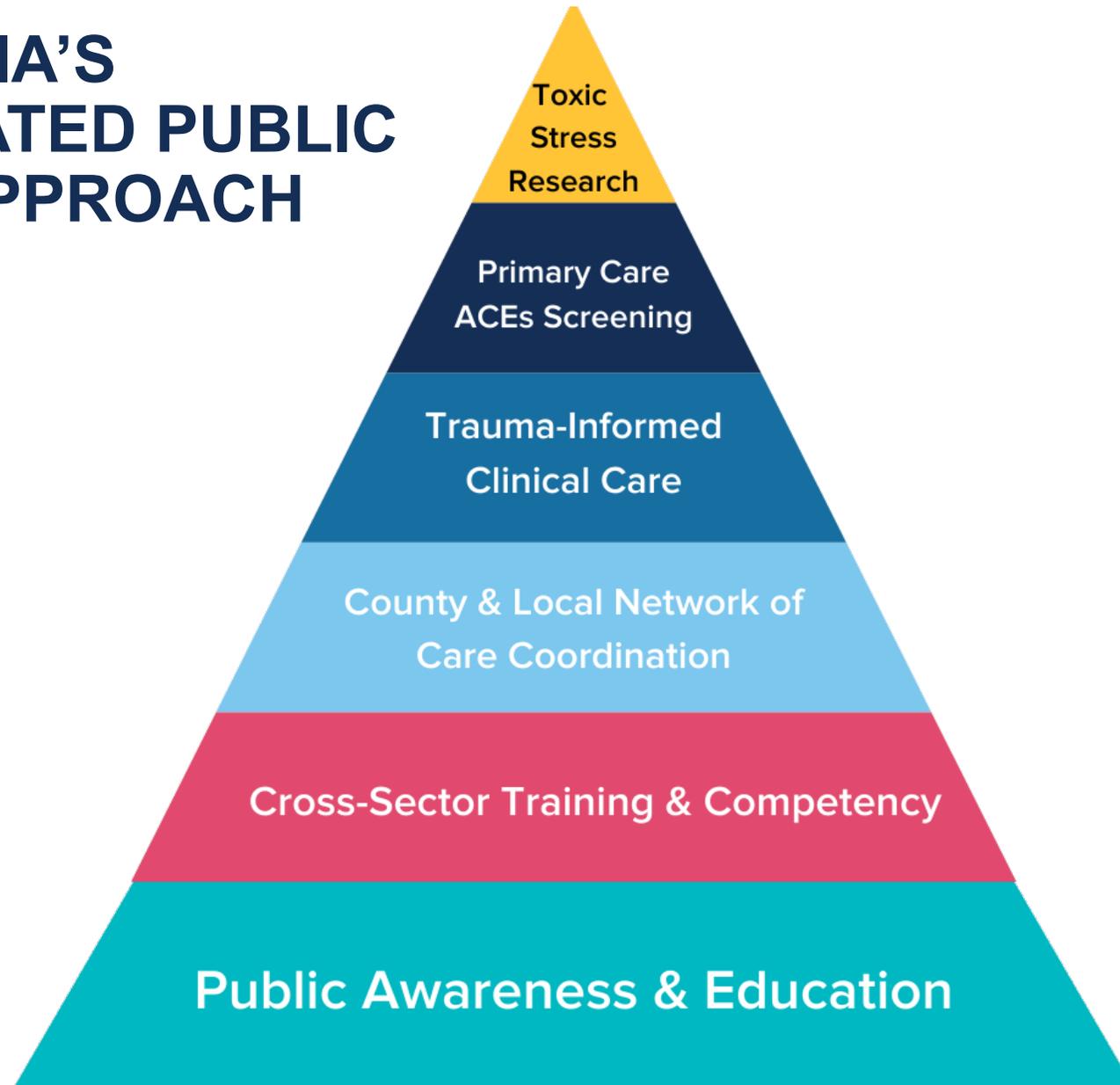


Healthcare	Public Health	Social Services	Early Childhood	Education	Justice
------------	---------------	-----------------	-----------------	-----------	---------

California's Foundational Response:

- **Establishing the 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

CALIFORNIA'S COORDINATED PUBLIC HEALTH APPROACH



Toxic Stress
Research:
California
Initiative to
Advance Precision
Medicine

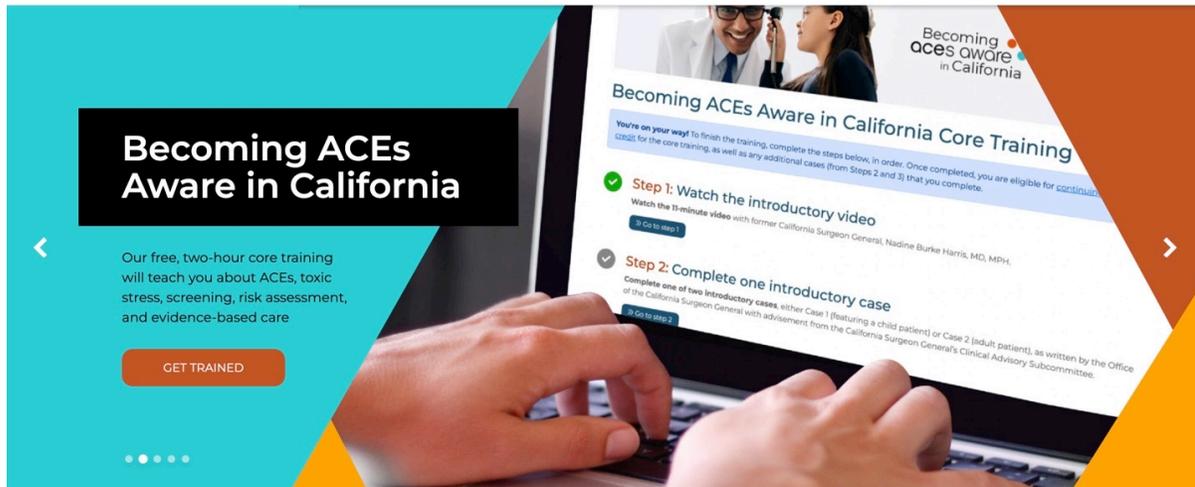
- **\$20M for 7 demonstration projects:**
 - **Children's Hospital Los Angeles:** *Scalable Measurement and Clinical Deployment of Mitochondrial Biomarkers of Toxic Stress*
 - **Loma Linda University:** *A Multi-Component Intervention to Strengthen Families and Build Youth Resilience*
 - **Stanford University:** *Systems-based, Multidisciplinary Assessment of Adversity and Toxic Stress for Individualized Care (The SYSTEMAATIC Project)*
 - **University of California, Irvine:** *Using Precision Medicine to Tackle Impacts of Adverse and Unpredictable Experiences on Children's Neurodevelopment*
 - **University of California, Los Angeles:** *Identifying Social, Molecular, & Immunological Processes for Mitigating Toxic Stress & Enhancing Personalized Resilience*
 - **University of California, San Diego:** *San Diego County, UC San Diego, & Community Partners Better Address ACEs with Precision Medicine & Organizational Change*
 - **University of California, San Francisco:** *The Collaborative approach to examining Adversity and building Resilience (CARE) Program*

Primary Care ACE Screening and Toxic Stress Risk Assessment



Events Grants Resources Blog About Contact Us **GET TRAINED**

ACE FUNDAMENTALS | LEARN ABOUT SCREENING | IMPLEMENT ACE SCREENING | PROVIDE TREATMENT & HEALING



The ACEs Aware initiative is a first-in-the-nation effort to screen patients for Adverse Childhood Experiences (ACEs) to help improve and save lives.

ACEs Aware strives to create a better world for our children, families, and communities by working together across sectors to prevent

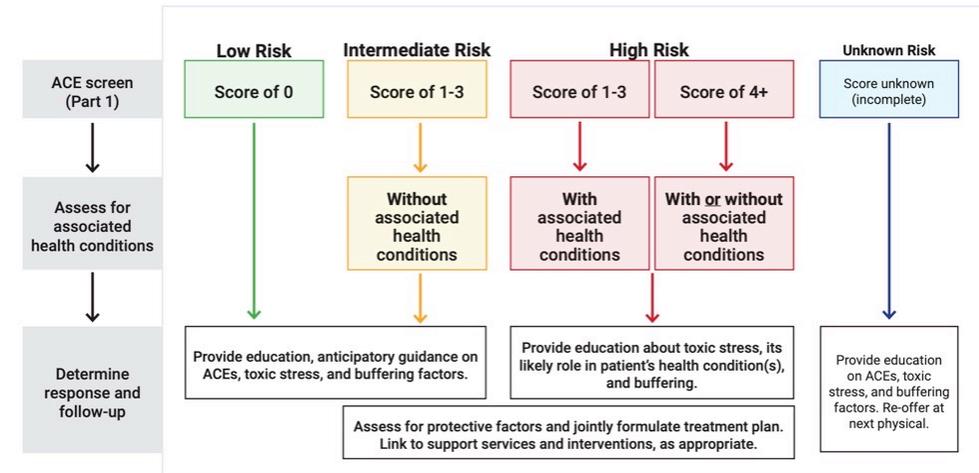
Sign-up to stay ACEs Aware

GET UPDATES



Adverse Childhood Experiences (ACEs) and Toxic Stress Risk Assessment Algorithm

Pediatrics



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.

Trauma Informed Clinical Care and Network of Care Coordination



Provide Treatment & Healing

A trauma-informed approach to addressing ACEs and toxic stress

- For Clinicians & Practices
- For Communities
- Stress Mitigation Strategies

This section describes strategies for clinicians, practices, and community organizations to build strong networks of care across the state. For information on clinical treatment of toxic stress, please visit the [Clinical Assessment & Treatment](#) page.

Trauma-informed networks of care form critical connections to cross-sector support

Sign-up to stay ACEs Aware [GET UPDATES](#)



CalAIM

<p>Behavioral Health Initiative</p> <p>Medi-Cal is strengthening mental health and substance use disorder services and better integrating them with physical health care.</p>	<p>Community Supports</p> <p>New services as part of the transformation of Medi-Cal help members address unmet basic needs that can impact their health, whether they're clinical or non-clinical. These include support to secure and maintain housing, and access to medically tailored meals to support short term recovery.</p>	<p>Dental Initiative</p> <p>Medi-Cal is expanding dental benefits for children and those with conditions that are more likely to lead to dental disease.</p>	<p>Enhanced Care Management</p> <p>Medi-Cal is providing high-need members with in-person care where they live.</p>	<p>Incentive Payment Program</p> <p>Medi-Cal is supporting the implementation and expansion of Enhanced Care Management, Community Supports and other initiatives by providing incentives to Medi-Cal managed care plans to invest in improving the quality of care, reducing health disparities, and promoting health equity.</p>	<p>Integrated Care for Dual Eligible Members</p> <p>Medi-Cal is better integrating care for members who are dually enrolled in both Medicare and Medi-Cal.</p>
<p>Justice-Involvement Initiative</p> <p>Medi-Cal is providing services to justice-involved adults and youth while they are incarcerated, and as they re-enter their communities.</p>	<p>Population Health Management</p> <p>Medi-Cal is requiring managed care plans to use a concentrated holistic approach to improving the health outcomes of a group of individuals.</p>	<p>Providing Access and Transforming Health (PATH)</p> <p>PATH funds are an investment in the capacity and infrastructure of local community-based organizations to provide services to Medi-Cal members in their communities.</p>	<p>Statewide Managed Long-Term Care</p> <p>Medi-Cal is introducing a better way to coordinate care for those with very complex or long-term care needs.</p>	<p>Supporting Health and Opportunity for Children and Families</p> <p>Medi-Cal is improving the health of children in California, supporting their families, reducing disparities in care, and strengthening accountability and oversight of children's services.</p>	

Cross Sector Training and Competency: Education



[ABOUT](#)

[PRIORITIES ▾](#)

[NEWS](#)

[RESOURCES ▾](#)

[CONTACT](#)



Safe Spaces

Foundations of
Trauma-Informed
Practice for
Educational and
Care Settings

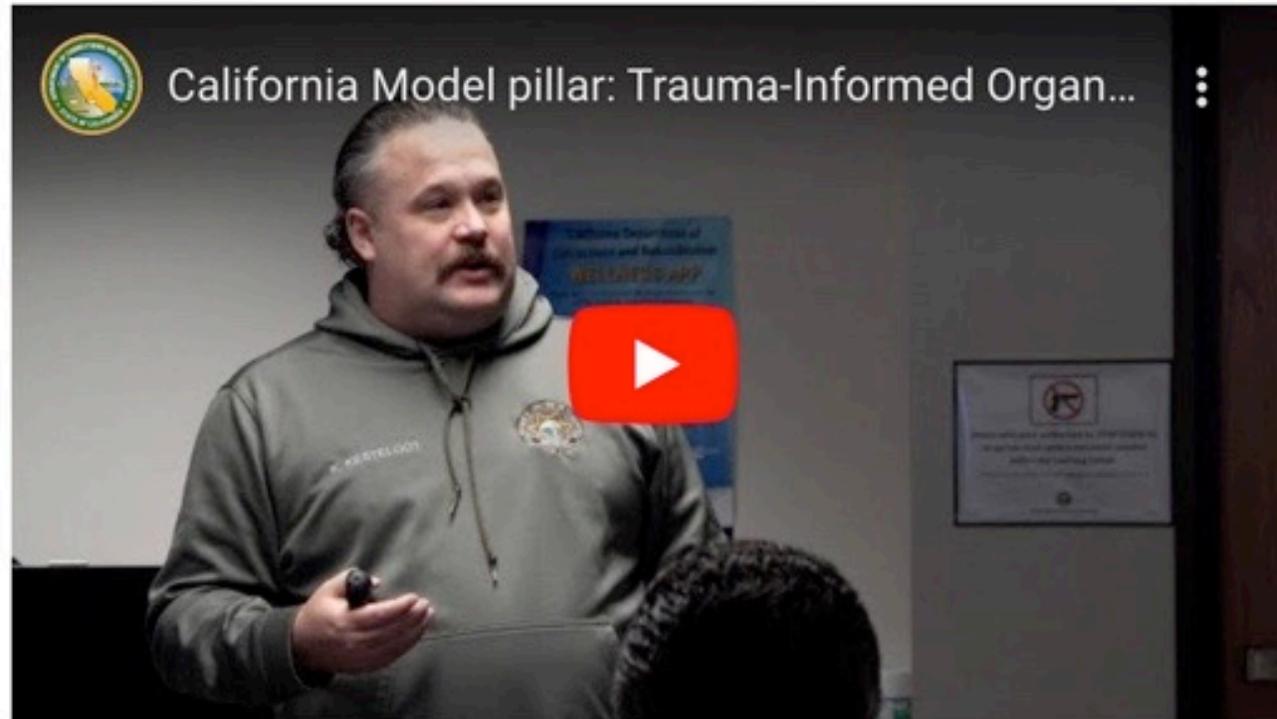


New Training Creates Safe Spaces for Kids

Safe spaces is a free, online training designed to help early care providers, TK-12 educators and other school personnel recognize and respond to trauma and stress in children.

TRAINING NOW LIVE!

Cross Sector Training and Competency: Corrections and Rehabilitation



Becoming a Trauma-Informed Organization: CDCR and CCHCS are committed to improving the practices, policies, and culture of the entire department by educating staff at all levels to recognize the impacts of trauma and ensure the physical and emotional safety of all staff and incarcerated individuals.

Public Awareness and Education

[Home](#)

[What is Toxic Stress?](#)

[Address Toxic Stress](#)



[Get Help Now](#)

[English](#)

[Español](#)

What is toxic stress?

When kids go through difficult or traumatic experiences, like losing a parent, getting bullied, or being exposed to violence, it can be very stressful on their minds and bodies. If this stress doesn't get addressed, it can build up and become toxic, which can lead to lasting challenges and serious health issues.



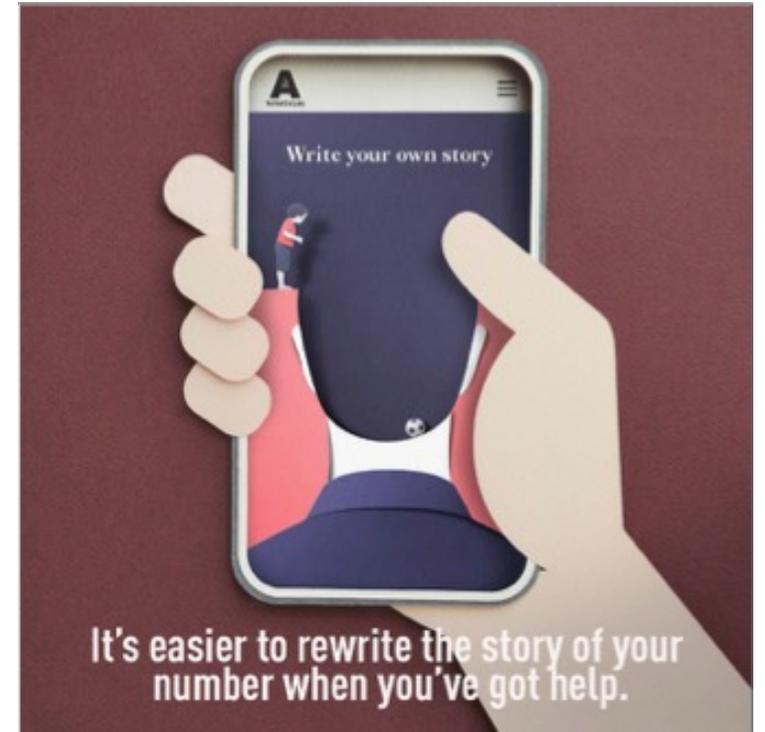
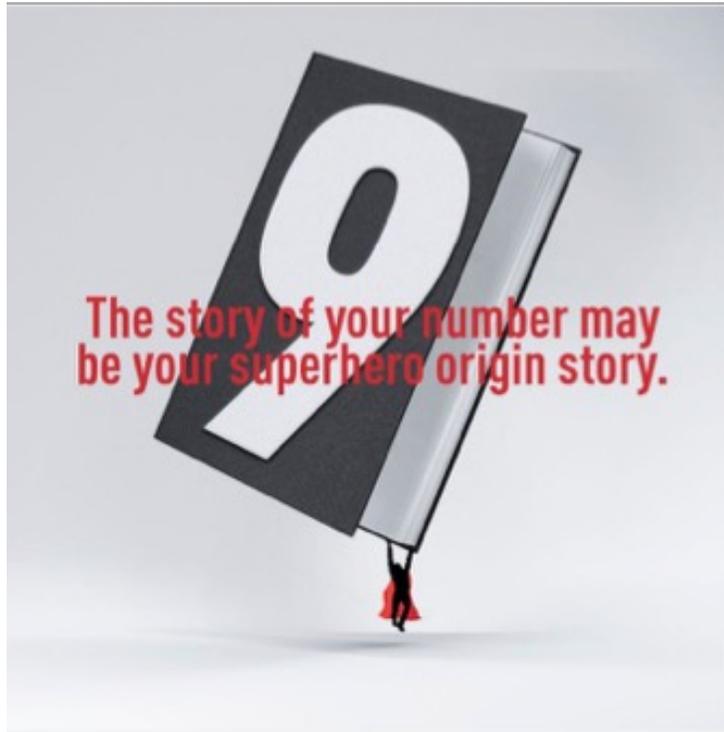
Public Awareness and Education

Our Key Audiences

-  **PRIMARY**
Youth and Young Adults (16-25)
-  **SECONDARY**
Caregivers
(emphasis on caregivers of youth ages 8-16)
-  **TERTIARY**
Health Care Providers, Educators, and Early Care Providers



Public Awareness and Education



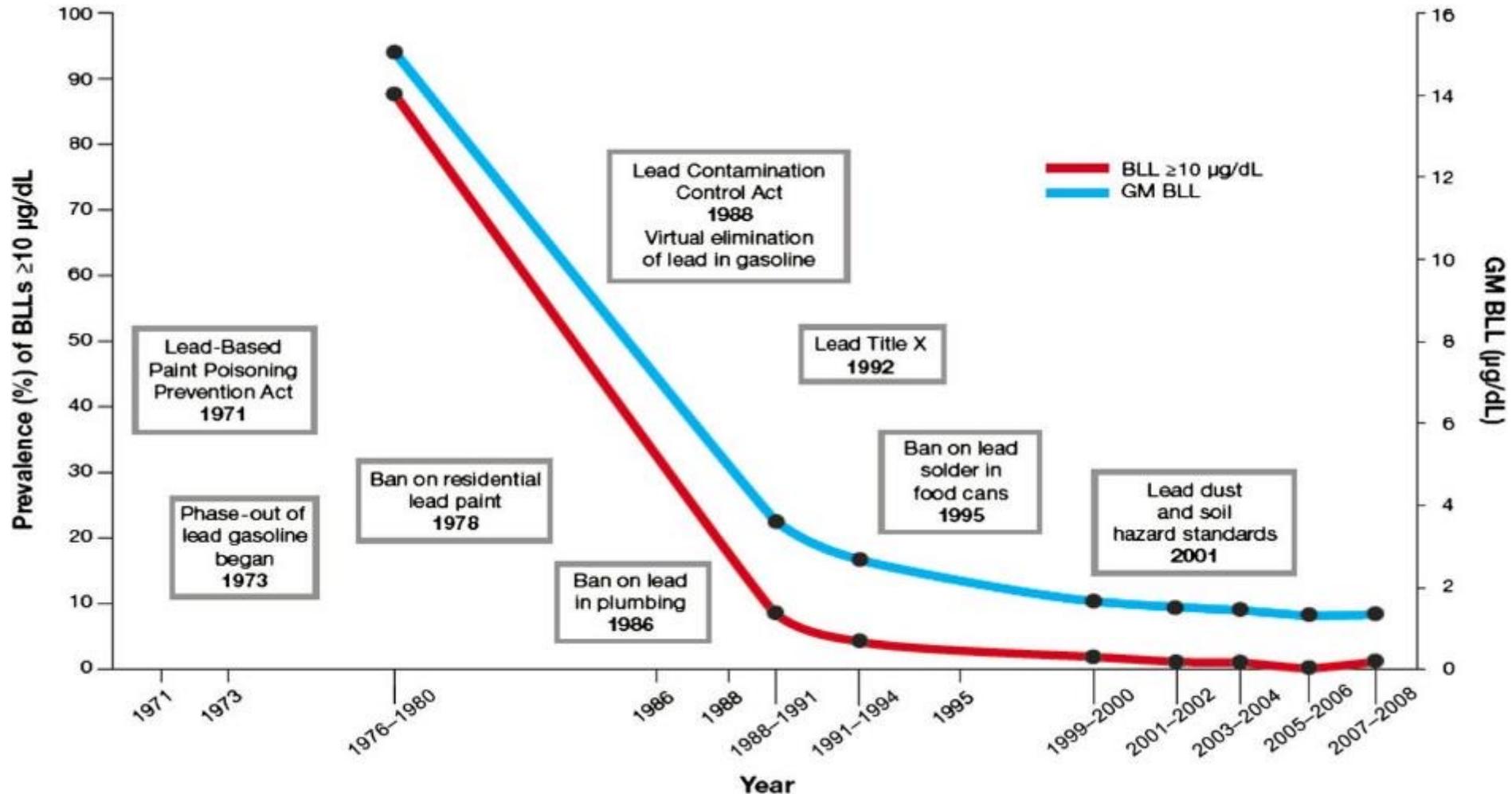
NUMBERSTORY.ORG

WE CAN

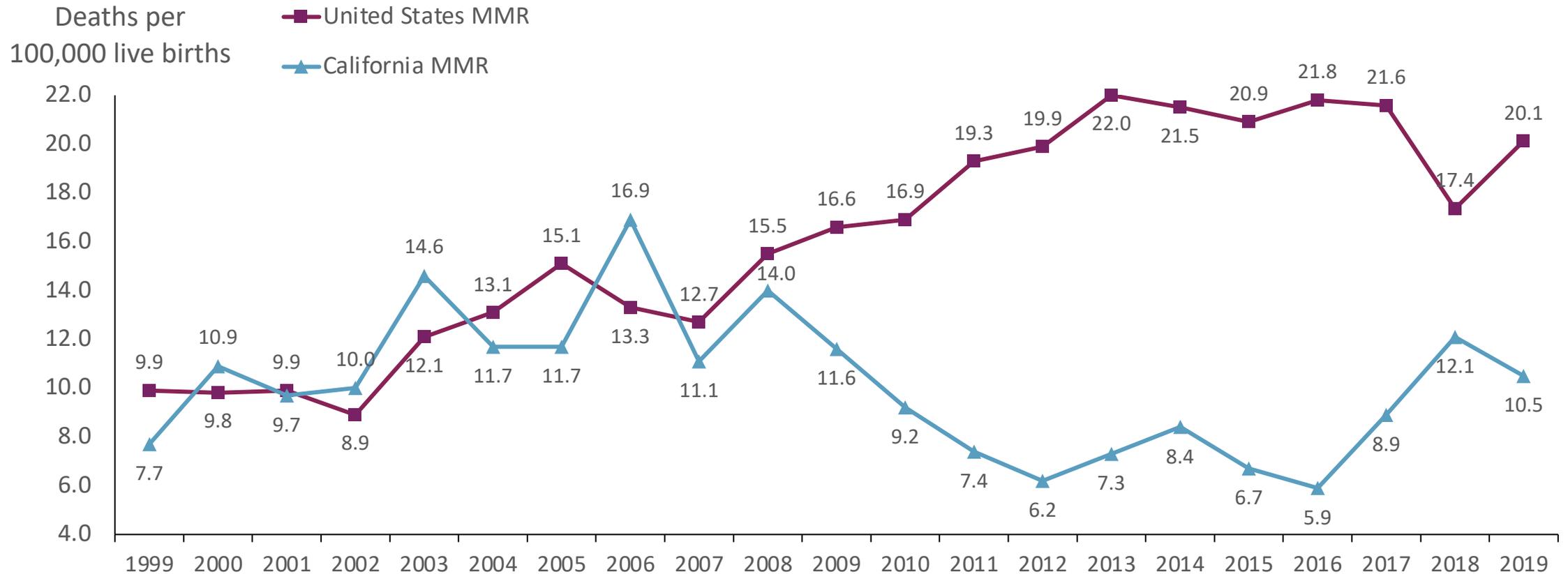
DO THIS!



Lead Exposure – Prevention approaches

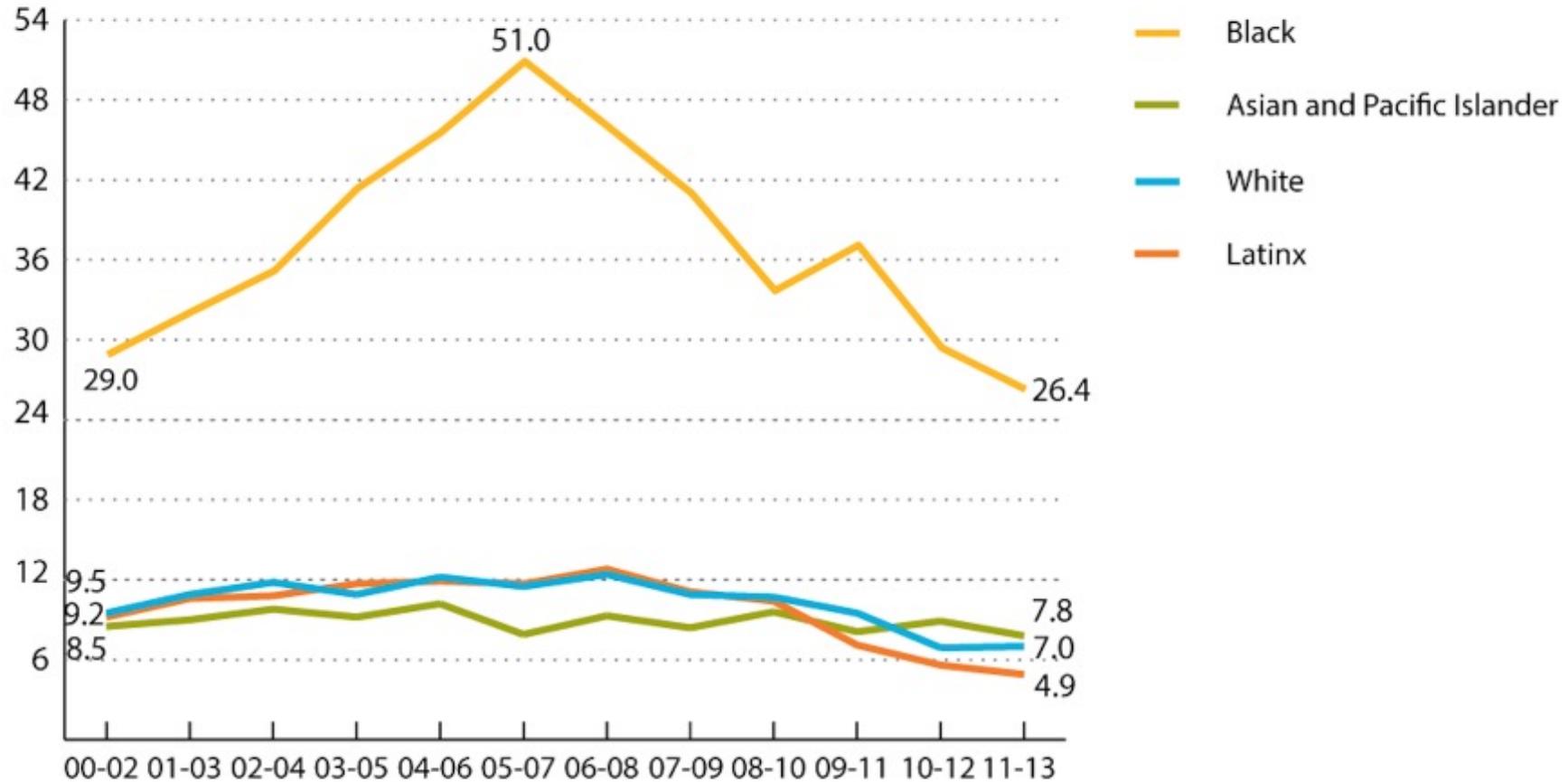


Maternal Mortality Ratio in U.S. and California, 1999-2019



Maternal mortality ratio (MMR) = Number of maternal deaths per 100,000 live births, up to 42 days after the end of pregnancy. Maternal deaths in California were identified using ICD-10 cause of death classification for obstetric deaths (codes A34, O00-O95, O98-O99) from the California death certificate data (1999-2013) and the California pregnancy status errata file (2014-2019). Data on U.S. maternal deaths are published by the National Center for Health Statistics and found in the CDC WONDER Database for years 1999 or later (accessed at <http://wonder.cdc.gov> on April 14, 2022).

Maternal Deaths per 100,000 Live Births



Note: Data reflect a three-year moving average. Race and ethnicity categories are mutually exclusive. Maternal mortality is defined as the death of a woman while pregnant or within 42 days of the end of pregnancy.

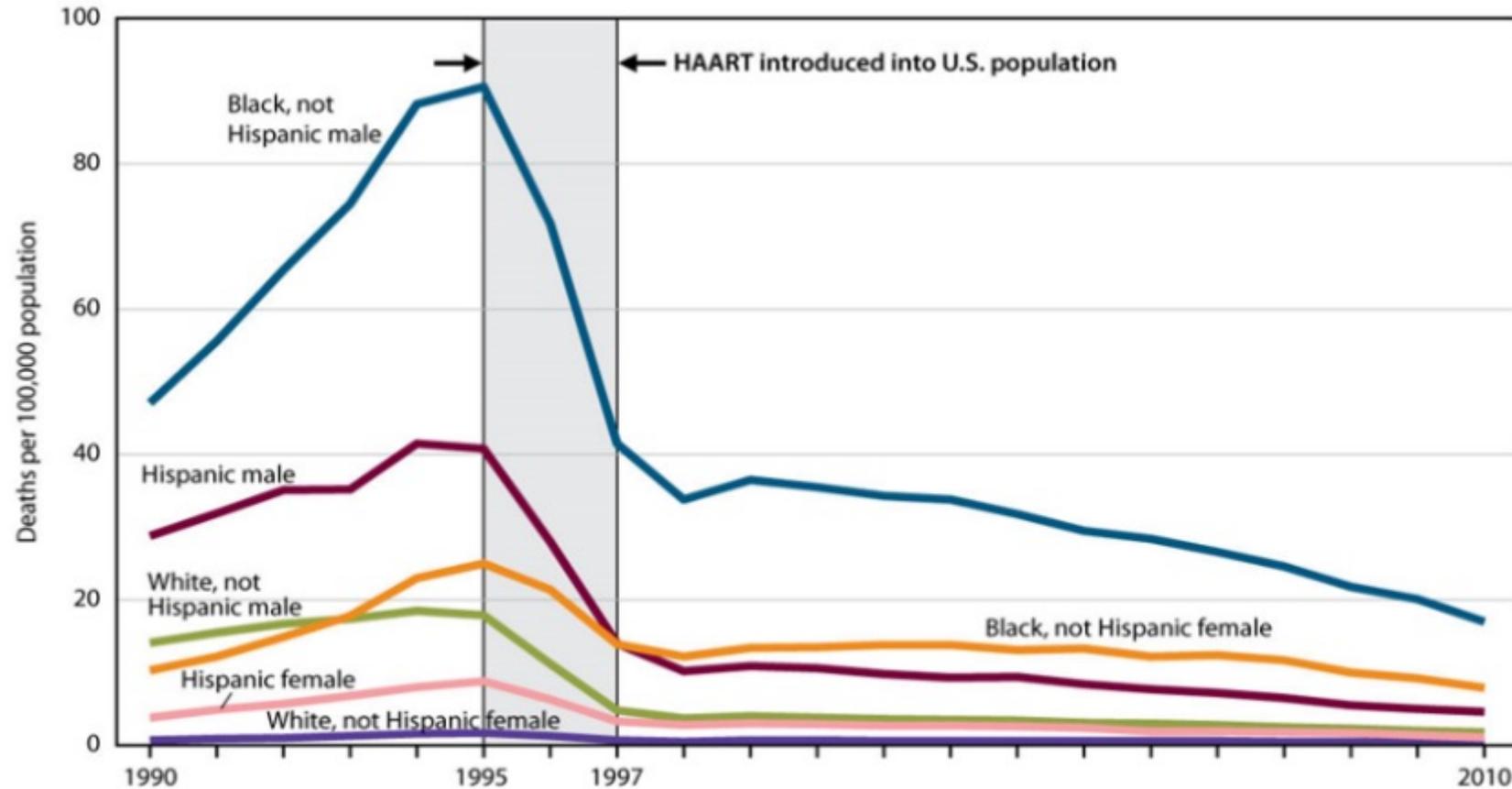
Source: California Department of Public Health



California Budget
& Policy Center

Independent Analysis. Shared Prosperity.

Death Rates for HIV Disease for all Ages



NOTE: HAART is highly active antiretroviral therapy.

SOURCE: CDC/NCHS, Health, United States, 2013, Figure 24. Data from the National Vital Statistics System.

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.

THANK YOU!
