

# Establishing Causality Between ACEs and Poor Health Outcomes

The Bradford Hill Criteria are widely used by the scientific community to establish causal inference from observational data.<sup>590</sup> Since their original publication in 1965, these criteria have been updated to incorporate modern molecular methods and data integration to strengthen the determination of causality.<sup>591</sup> These nine criteria can be definitively applied to the association between Adverse Childhood Experiences (ACEs) and poor health outcomes.<sup>5</sup>

## 1. STRENGTH.

**The stronger the association between the exposure and outcome, the more likely it is to be causal.**

There are strikingly strong associations between ACEs and many of the leading causes of death in the United States, ranging from 1.4 times the risk for diabetes to 37.5 times the risk for suicide attempt in those with four or more ACEs.<sup>2</sup> Individuals with four or more ACEs are two to three times as likely to develop ischemic heart disease, stroke, chronic obstructive pulmonary disease (COPD) and cancer, and 11 times as likely to develop Alzheimer's disease or other dementias, compared to those with no ACEs.<sup>2,16,17,30</sup> While the most robust associations are between ACEs and adverse neuropsychiatric outcomes, the links to adverse immune, metabolic, and cardiovascular outcomes are also quite strong,<sup>2,3,5,30</sup> equaling or exceeding the effects of other known causal factors. For example, the association between ACEs and ischemic heart disease equals or exceeds the effects of smoking and hypertension, depending on the dose (number of ACEs), and persists even after adjusting for traditional risk factors.<sup>592-594</sup>

## 2. CONSISTENCY.

**If multiple studies involving a variety of populations, locations, and methods demonstrate a consistent association, it is more likely to be causal.**

Findings from the Behavioral Risk Factor Surveillance System (BRFSS), which collects ACEs data from 42 states, show consistent associations between ACEs

and poor health.<sup>13</sup> These associations are further corroborated by global data from at least 17 countries.<sup>2</sup> The physiological effects and clinical consequences of ACEs are also consistent across study designs, from the original retrospective cohort ACE Study,<sup>3</sup> to prospective cohort studies,<sup>39,595</sup> to animal models in a variety of species.<sup>306,596</sup> There is also consistency across clinical, physiologic and molecular outcome measures. For example, the impact of ACEs and risk or protective factors on immune function has been documented clinically as increased risk of certain infections and autoimmune disorders,<sup>190,191</sup> physiologically as impaired immune responsiveness to vaccination,<sup>597</sup> and molecularly as alterations in inflammatory markers such as C-reactive protein, fibrinogen, and proinflammatory cytokines.<sup>340</sup> Together, these findings reinforce a consistent association between ACEs and immune dysregulation.

### **3. SPECIFICITY.**

**If the exposure leads to only one outcome, then the association is more likely to be causal.**

While it was previously thought that the association between ACEs and numerous health conditions undermined the criteria of specificity,<sup>5</sup> advances in science now point to the toxic stress response<sup>6,23,60</sup> as a single, highly specific mechanistic outcome of ACE exposure that consequently increases the risk of multiple negative health outcomes. Just as discovery of the role of the human immunodeficiency virus (HIV) in immune impairment shed light on the pathways that give rise to the many clinical manifestations of acquired immunodeficiency syndrome (AIDS), so too understanding of the toxic stress response sheds light on the mechanistic pathways underlying the associations between ACEs and myriad adverse health outcomes.

### **4. TEMPORALITY.**

**The exposure must precede the onset of the outcome in order for the association to be causal.**

The original ACE Study was based on adult participants' recollection of their ACE exposures,<sup>3</sup> which makes it challenging to establish temporality with certainty due to recall bias. However, multiple long-ranging birth cohort studies have since linked antecedent ACEs to the subsequent development of a variety of adverse health outcomes.<sup>39,595,598-600</sup> Prospective data showing that ACE-associated psychopathology in early adulthood mediates mid-life psychopathology also helps establish temporality.<sup>599</sup> A prospective study showed that childhood maltreatment predicts adult inflammation in a life-course study.<sup>176</sup>

## 5. BIOLOGICAL GRADIENT.

**If there is a dose–response relationship between the exposure and outcome, the association is more likely to be causal.**

The literature has consistently shown a dose-response relationship between the number of adversities experienced and almost all poor health and social outcomes studied.<sup>3,5,13,30</sup> For example, while individuals with four ACEs have double the risk of ischemic heart disease compared to those with none, those with seven or eight ACEs have more than triple the risk.<sup>5,9</sup> Similarly, compared to those with zero ACEs, individuals with one ACE have about 1.5 times the risk of respiratory disease, and those with four or more ACEs have more than 2.5 times the risk.<sup>30</sup>

## 6. PLAUSIBILITY.

**If there is a conceivable mechanism for the relationship given the current body of scientific knowledge, then the association is more likely to be causal.**

There are clear mechanisms through which ACEs harm health. ACE exposure in the absence of adequate buffering relationships and environments can lead to the toxic stress response, which is characterized by prolonged activation of the stress response via the hypothalamic-pituitary-adrenal (HPA) and sympatho-adrenomedullary (SAM) axes, leading to dysfunction of the neurologic, endocrine, immune, and metabolic systems and changes in DNA regulation.<sup>6,12,60,319</sup> These physiologic derangements can lead to a multitude of poor clinical outcomes. By affecting specific parts of the brain, such as the mesocorticolimbic system (reward centers),<sup>6</sup> toxic stress can also lead to health-harming behaviors, such as substance use, overeating, and sexual risk-taking.

## 7. COHERENCE.

**If the cause–and–effect story makes sense given the information available to the scientific community, then the association is more likely to be causal.**

The effects of ACEs on health fit with current knowledge of the biology of toxic stress, particularly when those ACEs occur during critical and sensitive periods of development in the absence of sufficient buffering relationships and environments.<sup>23,47</sup> The toxic stress response is defined in a 2019 consensus report by the National Academies of Science, Engineering, and Medicine as the “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.”<sup>23</sup> It includes neurologic, endocrine, immune, metabolic, and genetic/genetic regulatory derangements, and each mechanistic pathway involved coheres with the range of health consequences linked to ACEs via toxic stress.

## 8. EXPERIMENT.

**If manipulation of the exposure leads to changes in the outcome, then the association is more likely to be causal.**

While it would be unethical to introduce childhood adversity to demonstrate the cause-and-effect nature of ACEs and toxic stress, both natural experiments and animal studies have demonstrated a dose-response relationship between dose of adversity experienced and severity of outcomes.<sup>2-5,13,16,29,30,63,64,85</sup> Natural experiments, such as the 1998 Quebec Ice Storm and the Dutch Hunger Winter, show that prenatal exposure to stress leads to increased stress responsiveness and physiologically and clinically apparent changes in the immune, metabolic, and cardiovascular systems,<sup>421,601</sup> coherent with the effects of ACEs and toxic stress. Populations who have experienced the atrocities of war, such as Nazi prison camp refugees and Eastern Serbians exposed to civil war, have shown a higher incidence of autoimmune hyperthyroidism, which is coherent with the association between ACEs leading to toxic stress, and immune dysfunction.<sup>602</sup> Similarly, animal studies of rats and of rhesus monkeys demonstrate that experimental exposure to high doses of adversity, particularly during early development, leads to neuroendocrine, immune, metabolic, and genetic regulatory disruption.<sup>306</sup>

Conversely, there is robust experimental evidence that safe, stable, and nurturing relationships and environments can buffer the toxic stress response and mitigate the effects of ACEs.<sup>603,604</sup> The Bucharest Early Intervention Project, a randomized controlled trial among institutionalized infants and toddlers,<sup>605</sup> showed that early and stable placement in high-quality foster homes improved physiological and clinical outcomes in physical development,<sup>606</sup> brain structure and electrical activity,<sup>579,607</sup> and neuropsychiatric symptoms.<sup>608,609</sup> These findings are supported by many animal models. For example, Meaney and colleagues demonstrated that rat pups raised by more “attentive” mothers showed improved performance on cognitive tasks and better regulated stress responses as adults than those raised by less attentive mothers, and that these outcomes were associated with changes in epigenetic regulation of stress response pathways. Further, experimental manipulation in which the pups were switched at birth revealed that these findings, including epigenetic markers, were associated with the care of the rearing mother, even if the pups’ biological mothers were less attentive.<sup>306</sup> A population-based study documented that adults reporting ACEs were 72% less likely to experience

depression or poor mental health in adulthood if they also experienced positive childhood experiences (PCEs), defined as feeling safe to talk about feelings with your family, feeling supported in difficult times, having at least two non-parental adults to rely on, and having a sense of belonging in school or the community.<sup>41</sup> A study of US school-age children with ACEs similarly documents the mitigating effect of building family resilience and parent-child connection to substantially reduce the negative association of ACEs with diminished child resilience and lack of interest and engagement in learning and school.<sup>604</sup>

## 9. ANALOGY.

**If the exposure is similar to another exposure that has strong evidence for causing the outcome, then the association is more likely to be causal.**

High doses or long courses of corticosteroids are well documented to cause adverse health effects, such as impaired growth, delayed puberty, high blood sugar, obesity, hypertension, and neuropsychiatric symptoms. In fact, these effects are sufficiently predictable that clinical guidelines have been developed for monitoring and preventing them.<sup>60</sup> Thus, it is paradigmatically consistent that toxic stress, which leads to chronic dysregulation of cortisol (a natural corticosteroid) and other stress hormones, may cause similar hormonal, metabolic, cardiovascular, and neuropsychiatric outcomes in individuals who have experienced ACEs.<sup>86</sup>

In summary, rigorous application of the Bradford Hill Criteria strongly supports a causal association between ACEs, development of the toxic stress response, and a host of negative health and social outcomes.

Other potentially traumatic childhood experiences have been identified that may also increase the risk for toxic stress. These other potential traumatic childhood experiences incorporate the role of the community and social environments and recognize the experiences of diverse populations beyond the original ACE Study. Some of these risk factors are poverty, discrimination (particularly racial discrimination), food and housing insecurity, interpersonal and community violence, bullying, parental absence, death of a family member, child separation from the family, living in foster care, and justice system involvement.<sup>2,53-61</sup> They can coexist with and amplify the impacts of ACEs. We must continue to comprehensively evaluate and address other sources of early adversity to ensure that all children thrive in homes, communities, and social environments that are safe, stable, and nurturing.