https://doi.org/10.1038/s44220-024-00375-2

Risks and resilience — rewriting childhood adversity

Childhood adversity is a powerful driver of negative physical and mental health outcomes. Although major strides have been made in improving awareness of the potential consequences of adverse childhood experiences, they remain a common and entrenched public health concern linked with other health issues. New research may help to elucidate some of the neurobiological mechanisms associated with the experience of childhood adversity.

Oliver Twist, one of Charles Dickens' most popular and heralded books, was first serialized in a magazine in 1836. Each week, readers would eagerly consume the latest installment of the travails and mistreatment of its young protagonist, a poor orphan who begins his tale in a workhouse, enduring the many hardships of poverty — hunger, exploitation, crime and violence. Written and set in England in the Victorian era, *Oliver Twist* was based on Dickens' own experience of being forced to leave school at the age of 12 to work in a boot factory after his father was sent to a debtor's prison. The novel, like much of Dickens' other writing, was intended to be a vivid and forceful condemnation of the role of the class system in perpetuating systemic inequalities, featuring the most vulnerable and potentially disadvantaged people: children.

In the nearly 200 years since Dickens' accounts, there have been notable developments in societal orientation to the protection of children specifically. International commitments to the prohibition of hazardous child labor up to the age of 18, for example, have been made by the majority of the United Nations Member States. Since its adoption in 1989, the Convention on the Rights of the Child has codified the endorsement of access to education and healthcare for all children, appropriate legal and institutional assistance, protection for children's well-being, and protection from all forms of physical and mental violence.

Although it is crucially important to stipulate these protections at the societal and international levels, many gaps remain in legal protections for children. Despite increased awareness and study of childhood adversity, or adverse childhood experiences (ACEs), exposure to traumatic life events is widespread and represents a major and persistent public health issue. ACEs comprise multiple domains, including abuse (emotional, physical and sexual) and neglect (physical or emotional). A child's household environment can also present substantial exposure to ACEs, via a parent's or family member's problems with substance use or mental illness, intimate partner violence, incarceration, and parental separation or divorce.

Importantly, conditions of economic deprivation and social discrimination compound the prevalence and severity of ACEs. In the USA, for example, nearly two thirds of adults report the experience of a least one ACE during childhood, and nearly 20% of adults report the experience of multiple (four or more) ACEs — a percentage that jumps to nearly 30% in groups such as American Indian and Alaskan Native people, who have long experienced discrimination and inequality. In addition to race and ethnicity, which can lead to disproportionate exposure to ACEs, other factors such as sex and gender can also contribute. In studies of low- and middle-income countries in sub-Saharan Africa, for example, the majority of children and adolescents report multiple lifetime ACEs, most commonly physical violence, but the experience of sexual abuse occurs more commonly for girls. Children and adolescents who identify as sexual and gender minorities are also at increased risk of experiencing ACEs related to interpersonal discrimination, such as bullying, instability in housing, and increased alcohol and substance use.

The risks attributed to ACE exposure extend across a person's life. In addition to experiencing much higher levels of mental health conditions and suicidality, people with a larger number of ACEs are more likely to develop cardiovascular disease, stroke, diabetes and cancer. Beyond the increased burden of disease, there is an exceedingly great social and financial cost associated with ACEs. In North America and Europe, ACEs cost an estimated 37.5 million disability-adjusted life years or US $1.3 trillion annually, which indicates the potential for substantial social and economic gains by reducing exposure to ACEs.

Addressing and mitigating the enormous public health burden posed by ACEs is a multifactorial problem, and our comprehension of the specific pathways by which cumulative exposure perpetuates negative physical and mental health outcomes over the lifespan is limited. Existing research has connected models of stress biology in animals and humans with sociological and psychological frameworks of childhood adversity. Prolonged activation of stress responses in the absence of mitigating or protective factors, referred to as toxic stress, can lead to changes such as impaired immunity, increased inflammation, and dysregulated endocrinological and neurobiological function and development. ACEs are also consistently associated with an increased risk of psychiatric disorders in adolescence and adulthood, including post-traumatic stress disorder, anxiety and depression. Of the putative pathways involved in increased risk for psychopathology, recent work has highlighted epigenetic changes in response to ACEs during sensitive early-childhood periods.

One such process that may serve as a biomarker for adversity-related change at the molecular level is DNA methylation, whereby methyl groups are added to the DNA, typically at cytosine–guanine dinucleotides (CpGs), which can affect gene expression.

In the December 2024 issue of *Nature Mental Health*, we include a new study from Lussier and colleagues investigating epigenome-wide DNA methylation that mediates the association between the experience of childhood adversity and the development of depressive symptoms in adolescence. Using the Avon Longitudinal Study of Parents and Children and epigenomic data, the authors determined a subset of 70 CpGs that mediated the relationship between childhood adversity and depression in adolescence. The study also identified methylation differences at 39 CpGs that reduced the effects of adversity, which could be interpreted as being protective against subsequent development of depression. These are notable findings that speak to the potential of methylation as a biomarker not only for risk but also, potentially, for resilience.

Importantly, these insights into the changes that accompany exposure to childhood adversity are part of the emerging study of epigenetic patterns. Although this is conceptually intriguing, there is still much to be explored before epigenetic biomarkers can be applied in a clinically meaningful way, owing to numerous complexities, including changes in DNA-methylation patterns over the course of a person's life or developmental stage and the interplay with other, as-yet-unknown factors that shape whether some epigenetic changes may be protective.

The enormity of the impact of ACEs on physical and mental health underscores how important preventing childhood adversity is to broader public health efforts. In *Great Expectations*, Charles Dickens challenged readers with harsh truths about the indelible marks of poverty or abuse: "It may be only small injustice that the child can be exposed to; but the child is small, and its world is small…." Although these harsh truths are still relevant, with rapidly evolving research, advocacy and intervention, there is always new hope for mitigating and preventing childhood adversity.

Published online: 5 December 2024