Childhood adversity may cause epigenetic changes that increase or suppress depression risk

We showed, in multiple population-based birth cohorts, that blood-based DNA methylation partially explains the relationship between childhood adversity and adolescent depressive symptoms. DNA-methylation sites across the epigenome could explain an increased risk of depression but, unexpectedly, other sites also served as markers of resilience against the effects of childhood adversity on depression risk.

This is a summary of:
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The question

Childhood adversity is one of the most impactful determinants of physical and mental health across the life course, and greatly increases the risk of cardiovascular disease, depression and many other physical and mental illnesses[1]. Yet little is known about how this lifelong risk becomes biologically embedded during the first years of life. Epigenetic mechanisms such as DNA methylation have long been described as potential mechanisms that might mediate the relationship between early-life environments and mental health later in life[2]. Few studies have investigated the extent to which DNA-methylation patterns mediate or explain this relationship in human populations, particularly studies using epigenome-wide data. Although most mental health practitioners and research scientists would hypothesize that biological changes that result from childhood adversity increase the risk of depression (or other mental health disorders), no epigenome-wide studies have confirmed such relationships. Thus, we undertook a large-scale epigenome-wide investigation of whether DNA methylation can explain the relationship between childhood adversity and depression risk.

The discovery

We analyzed data from the Avon Longitudinal Study of Parents and Children, which allowed us to investigate longitudinal mediation through DNA methylation at an epigenome-wide level. Using these data, we first investigated the effect of seven common types of childhood adversity occurring during sensitive periods — developmental windows during which life experiences can have greater impacts on health outcomes — on depressive symptoms. We generally found that very early and early childhood adversity (at 0–3 and 3–5 years of age, respectively) had the greatest impact on the risk of adolescent depressive symptoms (at 10 years of age). We next investigated whether epigenome-wide DNA methylation, measured in blood obtained from children at 7 years of age, could explain the increased susceptibility to depression.

Using a novel two-stage analytical method[3], we identified DNA-methylation differences at 67 loci across the epigenome (70 total associations) that together explained 10–73% of the relationship between childhood adversity and depressive symptoms. Some of these epigenetic changes were related to increased depressive symptoms, in line with previous thinking about the biological embedding of risk. However, more than half of the 70 mediating associations were instead related to risk-suppressive effects on depressive symptoms (Fig. 1). In other words, these childhood-adversity-induced DNA-methylation changes were protective against depressive symptoms (they lowered the risk of adolescent depression). Perhaps most importantly, in independent birth cohorts — from the Generation R Study and Future of Families and Child Wellbeing Study — DNA methylation's unexpected protective role in the relationship between childhood adversity and depressive symptoms was more strongly replicated than was its expected risk-increasing role. Taken together, these findings may reflect a biological mechanism for the effects of childhood adversity on future mental health.

The implications

This study used epigenome-wide data to show that DNA methylation mediates, or partially explains, the relationship between various forms of childhood adversity and adolescent depressive symptoms. Our findings demonstrate that DNA methylation can act as both an indicator of depression risk and a potential marker of resilience against the effects of childhood adversity on depression. These results also highlight the biological mechanisms through which childhood adversity might influence adult mental health, potentially revealing future therapeutic targets.

Several factors should be considered in interpreting these results. We focused on epigenetic changes in blood, a peripheral tissue that may not be the main causal mechanism that links childhood adversity to depression, a chiefly brain-based disorder. Thus, these epigenetic alterations may reflect the underlying biological changes that modify the risk of depression, without being its direct cause. In colloquial terms, the changes identified may be the smoke, not the fire.

We also hope future studies will replicate our findings in other groups of children, adolescents or adults, as we and others have shown that DNA-methylation patterns show time-varying associations with childhood adversity[4]. Should our findings be replicated, these epigenetic alterations could potentially be used as biological indicators of risk of and resilience against depression across the life course. Ultimately, this research may spur new strategies for preventing depression, other kinds of mental illnesses and physical disorders that often occur after exposure to childhood adversity.

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EXPERT OPINION

"While it is well established that childhood adversity substantially increases susceptibility for depression, the exact underlying mechanisms remain unknown. Lussier et al. investigate if DNA methylation may act as a possible mediator in this association. Their study underscores the power and importance of longitudinal designs and strengthens the hypothesis that DNA methylation reflects a biological pathway for the embedding of adverse childhood events." **Darina Czamara, Max Planck Institute of Psychiatry, Munich, Germany.**

FIGURE

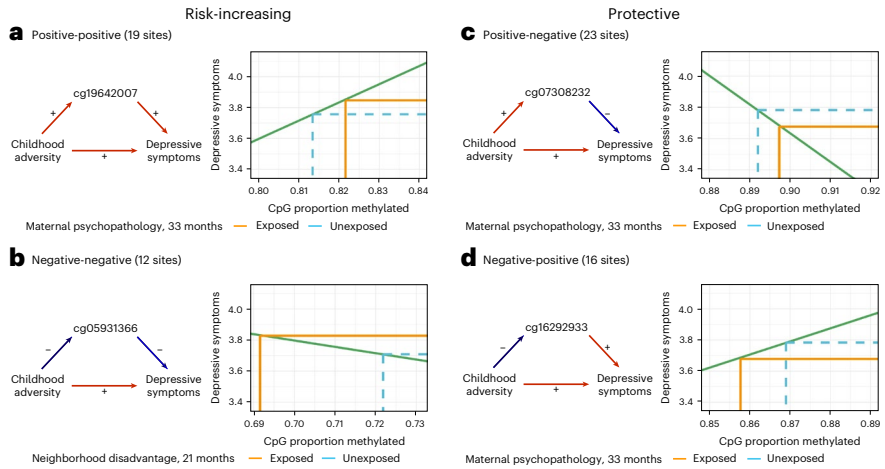

Fig. 1 | Risk-increasing and protective mediation patterns. We identified four mediation patterns (left side of each panel, for a representative CpG mediator) for the relationship of childhood adversity (at 21 or 33 months of age), DNA methylation at 67 CpG sites (at 7 years of age) and depressive symptoms (at 10 years of age). The mean difference in DNA methylation (CpG proportion methylated) in response to exposure to childhood adversity (maternal psychopathology or neighborhood disadvantage) and its relation to depressive symptoms (plots at right) is unique for each pattern across the 70 associations identified. Two patterns (positive-positive (**a**) and negative-negative (**b**)) showed that DNA methylation had a risk-increasing role, whereby epigenetic changes from exposure to childhood adversity resulted in greater depressive symptoms. The two other patterns (positive-negative (**c**) and negative-positive (**d**)) showed that DNA methylation had a protective role, whereby adversity-induced epigenetic changes resulted in fewer depressive symptoms.

BEHIND THE PAPER

The most interesting moment in this project was when we discovered that mediation patterns reflected resilience against depression, rather than just risk (Fig. 1). We did not expect this finding, as it contrasted with our commonly held assumptions about the biological embedding of risk through DNA methylation. At first, we were uncertain what to make of the different mediation patterns. However, our results began to take shape once we replicated them in additional birth cohorts: the Generation R Study, and the Future of Families and Child Wellbeing Study. We were further energized when we found, in a parallel study, that adversity-associated DNA-methylation changes could be protective against physical and mental illness[5]. Ultimately, these multiple lines of evidence made us more confident that these patterns were real and might reflect a novel paradigm for epigenetic alterations in linking early-life environments to human health. **A.A.L. & E.C.D.**

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   This paper reports on the relationship between adversity-associated epigenetic changes and physical or mental illness.

FROM THE EDITOR

"It has long been known that childhood adversity, such as childhood maltreatment, increases the risk of depression and other mental health disorders. This article provides a compelling account of the role of epigenetic changes via DNA methylation in cytosine–guanine dinucleotides that mediate the relationship between the experience of childhood adversity either by increasing risk or by increasing resilience." **Rebecca Cooney, Chief Editor, *Nature Mental Health*.**