Trauma and stress, particularly in early life, can have long-lasting implications on health and well-being throughout the life course. Adverse childhood experiences (ACEs), such as abuse, neglect, and challenges in the household or family before the age of 18 years, have been associated with adverse health-related behaviors, mental health conditions, and increased risk of illnesses, including diabetes, cardiovascular disease, and cancer. The effects of psychosocial stressors may extend across generations, affecting the children and grandchildren of individuals directly affected, through non-genetic intergenerational or transgenerational inheritance. There is a growing body of literature investigating how the cascade of physiological responses to adversity contributes to the biological embedding of ACEs. Epigenetic markers, including DNA methylation, may be involved in linking ACEs to health through programming of immune regulation, neurodevelopment, and the hypothalamic-pituitary-adrenal axis in response to stress and trauma. The effects of ACEs may also be reflected in changes to aging-related pathways recapitulated by epigenetic clocks, or biomarkers of biological aging calculated using DNA methylation levels.

Dye et al. investigated associations of preconception ACEs experienced by mothers with epigenetic age acceleration in pregnancy and in their children at birth, using data from 883 of 1018 mother-child pairs in the Accessible Resource for Integrated Epigenetic Studies (ARIES) substudy of the Avon Longitudinal Study of Parents and Children (ALSPAC). Maternal ACEs were evaluated by retrospective self-report, and a total ACE score of 0 to 10 components was used as the exposure. Epigenetic age acceleration, or the difference between epigenetic age and chronological age, was calculated for mothers during pregnancy and newborns. Total maternal ACE score was positively associated with epigenetic age acceleration during pregnancy, measured with the GrimAge clock ($\beta$, 0.22 [95% CI, 0.12-0.33] years). Additionally, individual ACE components were associated with greater epigenetic age acceleration (measured with GrimAge and PhenoAge) and pace of aging (measured with DunedinPACE) in mothers, with the association of physical neglect with GrimAge having the largest effect size ($\beta$, 1.53 [95% CI, 0.31-2.74] years). Individual ACE components were similarly associated with epigenetic gestational age acceleration in newborns, although the associations differed between sexes.

The findings by Dye et al. support previous studies linking adverse experiences to health. Epigenetic age acceleration has been demonstrated to be a robust biomarker of downstream health outcomes at multiple life stages. By analyzing multiple epigenetic clocks, the authors were able to identify potential nuances in the associations of ACEs with health. For example, GrimAge and PhenoAge are second-generation epigenetic clocks trained on aging-related biomarkers and phenotypes that can predict morbidity and mortality in adults, whereas the gestational age clock was developed to estimate gestational age and developmental maturity at birth. Moreover, the study by Dye et al. supports the hypothesis that preconception ACEs may affect the fetal environment, as suggested by changes in maternal epigenetic aging, and that intergenerational effects of trauma may be conveyed through perturbations in epigenetic programming. In several previous studies, parental ACEs have similarly been associated with offspring DNA methylation and epigenetic aging. Studies using biological samples collected at birth, as in Dye et al., may be particularly informative to distinguish between the effects that parental ACEs may have during fetal development, a time of epigenetic reprogramming, and the effects of related psychosocial exposures later in childhood.

However, the advancement of epigenetic clocks to investigate the effects of trauma and other psychosocial factors on health requires further development and understanding of these biomarkers.
In particular, epigenetic clocks are understudied in pediatric populations, and it is currently unknown whether increased epigenetic age acceleration at birth or in children is indicative of the same health risks observed in adults. Arguably, a full-term gestational age is more beneficial than a premature one at birth, but it is unclear whether greater epigenetic age acceleration measured by gestational age or life-course clocks may also be beneficial to birth outcomes and health in childhood, adolescence, and later life stages. Overall, epigenetic clocks developed to estimate gestational age have also been limited by small training sets, which may affect their performance in diverse populations, particularly those at the greatest risk of ACEs and adverse psychosocial experiences at other life stages.

Furthermore, there is limited understanding of the biological factors underpinning variation in epigenetic age. The observation that associations between maternal ACEs and epigenetic gestational age acceleration differ between male and female newborns highlights the need for additional research on the role of sex as a modulator of the association of environmental and psychosocial exposures with epigenetics. Fetal sex may place differential stress on mothers (eg, male sex related to greater metabolic demand and inflammatory response), which may modify the association between early life adversity and epigenetic aging. Maternal epigenetic age may also be associated with gestational age at sample collection due to the highly dynamic nature of the immune system during pregnancy; therefore, a single measurement may not be representative of epigenetic age acceleration. Associations of maternal adversity with offspring epigenetic age may also differ by tissue. As the interface between mother and child, the placenta may have distinct epigenetic responses to changes in the fetal environment. Additionally, intergenerational epigenetic effects, including those related to parental ACEs, may be conveyed through the male germline, although study of paternal exposures has been limited.

In recent years, the development of DNA methylation-based biomarkers has been prolific, leading to a broad range of novel estimates of aging, mortality, disease diagnosis and prognosis, health-related exposures, and stress response. These DNA methylation-based biomarkers have commonly been developed in the blood and in other noninvasive surrogate tissues, contributing to their broad application in research settings. Although clinical applications of epigenetic biomarkers are nascent, there is increasing evidence that epigenetic biomarkers may have utility in the fields of psychology and psychiatry. Such measures may serve not only as biomarkers to aid in the diagnosis of psychiatric disorders but also as a biomarker of past trauma, including that experienced by previous generations. Leveraging epigenetic signatures of trauma may help to identify individuals at risk and to target interventions aimed at addressing the effects of intergenerational trauma. In addition, due to the dynamic nature of epigenetic markers, biomarkers such as epigenetic clocks may be used to help understand factors associated with susceptibility and resilience to stress and trauma and to evaluate the efficacy of trauma-focused therapy and interventions.

Epigenetic biomarkers are promising tools for understanding and mitigating the long-term health effects of trauma and other psychosocial exposures. The study by Dye et al contributes to the evidence that epigenetic pathways are involved in linking adverse experiences to health within and across generations. As the fields of both epigenetics and trauma research advance, future studies should focus on identifying relevant and specific biomarkers linking trauma to health, similar to second-generation epigenetic clocks that have been developed for aging-related phenotypes, which may be translated to clinical settings to improve trauma-informed care.
Author Affiliations: Department of Epidemiology and Population Health, Stanford School of Medicine, Palo Alto, California (Bozack, Cardenas); Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown University, Providence, Rhode Island (Merrill); Department of Pediatrics, Stanford School of Medicine, Palo Alto, California (Cardenas).

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by grants K99ES035109 (Dr Bozack) and ROI ES031259 from the National Institute of Environmental Health Sciences (Dr Cardenas) and grants R01 MD015401 and R01 MD016595 from the National Institute on Minority Health and Health Disparities.

Role of the Funder/Sponsor: The funders had no role in the analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES


Downloaded from jamanetwork.com by guest on 08/11/2024