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Invited Commentary | Equity, Diversity, and Inclusion

Statistical and Conceptual Considerations in Socioepigenomics Research on Childhood Adversity and Epigenetic Aging

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Applications of epigenetic clocks to health questions have proliferated over the past decade, particularly as a means of understanding disease etiology. Epigenetic clocks are aggregate biological markers associated with aging that are derived from DNA methylation (and sometimes trained on other health measures, including mortality) and provide a biological indicator associated with accelerated or decelerated aging. Over the last 10 years, these clocks have been increasingly applied as outcome measures in studies of childhood adversity and other early life stressors, with the goal of investigating whether divergent biological aging may be a pathway explaining long-term health outcomes associated with adversity. If supported by empirical evidence, this knowledge may pave the way to personalized clinical care for people with histories of childhood adversity. It may also lead to population-level efforts for risk stratification so that public health interventions may be targeted to groups most in need.

The study by Kim et al[1] makes an important contribution to the literature in advancing research on the biological embedding of childhood adversity. The authors analyzed data from the Coronary Artery Risk Development in Young Adults (CARDIA) longitudinal cohort to investigate the association between a subset of adverse childhood experiences (ACEs) and 5 biomarkers associated with epigenetic age acceleration (EAA) at 2 time points in middle adulthood, a developmental period understudied in epigenetic aging research on ACEs. Although point estimates were consistently positive (ACEs were associated with accelerated epigenetic age), the magnitude of the mean difference in EEA associated with ACEs varied with the clock examined. The largest magnitude was detected for the GrimAge epigenetic clock. For this clock, the study authors found that adults who retrospectively reported having experienced 4 or more ACEs were a mean of 1.52 years older on an epigenetic level than their peers who had experienced fewer than 4 ACEs after adjusting for demographic factors. This finding is notable given that these ACEs would have occurred more than 20 years prior to the measurement of EAA. This suggests that imprints of childhood adversity may be detectable in the epigenome even decades later.

Results from this study bring much needed attention to health outcomes associated with childhood adversity and how epigenetic clocks may be used to understand biological associations between adversity and later health outcomes. This study also draws attention to several statistical and conceptual points, which are key for socioepigenomics research.

First, this study illustrates the complexity of covariate adjustment, a topic we described extensively in our work examining indicators associated with socioeconomic position as possible confounding factors in epigenetic analyses.[2] We applaud the authors for presenting their results in step-by-step stages, with covariates added sequentially to regression models that grew to include more variables. The story that unfolded from these sequential approaches was that results may be heavily impacted by the choice of included covariates. Such insights may be informative for future studies, including those seeking to replicate prior findings. These step-by-step results also allow researchers to triangulate findings by distinguishing associations specific to a given data set and those that may generalize across contexts and population groups.

However, some later step-by-step results presented by Kim et al[1] may be very conservative and possibly biased toward the null. The authors note that "subtle variations between models with and without adjustment for health-related behaviors and SES [socioeconomic status] in adulthood

suggest that individuals with ACEs may have had an increased risk of accelerated biological aging, even with healthy behavior or social achievement in adulthood."[1] However, some health-related behaviors and adult markers associated with socioeconomic position included in regression models 3 and 4 were possibly unnecessary to include; these measures were unlikely to meet the definition of a statistical confounder, at least in this study, for at least 2 reasons: (1) The number of ACEs was not associated with body mass index, daily alcohol consumption, or physical activity[2]; thus, there was no association between exposure and these possible confounders in this study's data. (2) Although the number of ACEs was associated with smoking status (children exposed to ≥4 ACEs were more likely to smoke relative to their peers), smoking likely reflects an exposure temporally subsequent to ACEs. Thus, it was more likely a possible mediator than confounder in the ACEs and EAA association. Given these considerations, readers may want to prioritize results from model 2.

Second, longitudinal studies of EAA are becoming more common, and it is crucial to choose appropriate statistical models, such as generalized estimating equations (GEE) and mixed models. We commend the authors' GEE approach to model their longitudinal data. Furthermore, they correctly adjusted for chronological age in their models. A 2023 study[3] found that failing to adjust for age in models of EAA may bias results toward the null.

However, some alternative modeling choices may have been considered. Kim et al[1] calculated change in EAA before modeling this as an outcome. Another, potentially more powerful approach may have been to include an interaction between age and ACEs in the GEE. Furthermore, to allow for between-individual variation in change in EAA, a linear mixed model with a random slope may have been used alongside this interaction.

Third, a limitation briefly discussed by the authors is the absence of parental mental illness and other adversities in the construction of ACEs scores. Given substantial heritability estimates of mental illness combined with the observation that mental illness is associated with premature mortality, ACEs measures that include parental mental illness may be associated with even greater changes in EAA in midadulthood. Relatedly, if attrition was also patterned by ACEs exposure, as we would hypothesize, this may also suggest that mean differences in EAA associated with ACEs could be greater than what was reported. Imputing missing data may account for a likely association between attrition and ACEs, which could further increase effect sizes.

Fourth, an underexplored area in the field and a topic not examined in this paper relates to dosing effects of childhood adversity exposure. Many authors have challenged the use of ACE counts[4] in favor of models that group exposures by conceptual subtype or the developmental timing of their occurrence.[5] For example, robust evidence now suggests 2 findings: (1) Associations of adversity with DNA methylation may be time dependent, with exposures in early childhood rather than recency of exposure or an accumulation of exposures across time associated with DNA methylation.[6] (2) Epigenetic associations may change dynamically, with different outcomes in various health domains across development.[7] We commend Kim et al[1] on considering 2 epigenetic time points in adulthood and hope that future studies with at least 3 time points across the life course may build on this study's findings on exposure counts by examining these additional dimensions of adversity and timing within a longitudinal framework.

Fifth, epigenetic studies need to uncover the extent to which associations of adversity with DNA methylation reflect causal signatures of adversity exposure and perhaps function as biological mechanisms through which adversity "gets under the skin." By continuing to collect longitudinal data from well-characterized epidemiological samples, we may better understand these complex associations and ultimately translate these findings into novel interventions that may mitigate outcomes associated with adversity exposure across the life course.

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