JACC: BASIC TO TRANSLATIONAL SCIENCE VOL. 9, NO. 5, 2024

EDITORIAL COMMENT

Early Life Cardiovascular Risk Factors and Midlife Epigenetic Aging

An Enduring Legacy*

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Aging can be seen as a progressive deterioration of our physiological functions. Although a person's chronological age based simply on their date of birth is a strong predictor of this process, there can be interindividual differences in the speed at which biological aging occurs. To capture such interindividual differences, several composite epigenetic markers have been developed that combine the DNA methylation status of multiple sites across the human genome to predict age-related traits. The first-generation measures of epigenetic aging, such as the ones developed by Horvath[1] and Hannum et al,[2] were derived by regression models that merely predict chronological age, whereas second-generation measures, such as the widely used PhenoAge and GrimAge, further predicted health span and lifespan by including in their regression health and mortality endpoints.[3,4] For all these markers, the degree to which epigenetic age outpaces chronological age—that is, the individual's "epigenetic age acceleration"—is used as a measure of biological aging.

Following these developments, an exponentially increasing number of studies have repeatedly found associations between accelerated epigenetic aging and a variety of age-related traits, independent of chronological age.[3] For example, studies have shown cross-sectional associations between epigenetic age acceleration and cardiovascular risk factors.[5] Epigenetic aging has also been associated with measures of subclinical atherosclerosis and with risk of incident clinical coronary heart disease.[6] What has remained understudied, however, is whether cardiovascular risk factors early in life can result in enduring effects on epigenetic age acceleration that are still detectable later in life.

In this issue of *JACC: Basic to Translational Science*, Sun et al[7] provide novel insights into this research gap. The investigators used the Bogalusa Heart Study, a population-based, prospective cohort study that has followed 1,580 participating children from 1973 onward. They studied cardiovascular risk factors during childhood in relation to epigenetic age acceleration in midlife. They found that unfavorable metabolic profiles in childhood, including increased body mass index (BMI), systolic blood pressure, and triglycerides, and decreased high-density lipoprotein cholesterol, predicted midlife epigenetic age acceleration, as measured with 3 of the 4 aforementioned markers (Hannum, PhenoAge, GrimAge). They performed cross-lagged panel analyses, a well-suited and sophisticated approach for clarifying temporal relationships, thereby providing evidence that BMI, triglycerides, and high-density lipoprotein cholesterol are more likely to be determinants rather than consequences of epigenetic age acceleration. The investigators further found that cardiovascular risk factors during childhood were associated with carotid intima media thickness, a measure of subclinical atherosclerosis. They found that PhenoAge and GrimAge mediated up to 27% of the associations of BMI and triglycerides with subclinical atherosclerosis. Together these findings extend prior work and suggest a temporal relationship and potential causal

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2452-302X https://doi.org/10.1016/j.jacbts.2024.02.006

pathway through which cardiovascular risk factors early in life can exert enduring effects on epigenetic aging, thereby contributing to atherosclerosis risk later in life.

Although the study by Sun et al[7] provides valuable insights, it also reveals lingering questions that should be clarified by future research. First, although the longitudinal design reduces the likelihood of reverse causation, these analyses may still be vulnerable to confounding. Orthogonal approaches for causal inferences such as Mendelian randomization for time-varying exposures could further support and clarify the underlying causal relationships.[8] Second, it is unclear whether the observed association and mediation is explained by an overall effect on biological age or a more specific effect on epigenetic age. This question is relevant because different markers of biological aging have been suggested to have independent or even additive effects on disease risk.[9] To better characterize such effects, future studies should integrate epigenetic with other established measures of biological age such as telomere length and proteomic age. Finally, the investigators used carotid intima media thickness as a measure of subclinical atherosclerosis. Given that carotid intima media thickness is not a particularly strong predictor of clinical events, it would be worthwhile to demonstrate this same mediation by epigenetic age acceleration with other measures of atherosclerosis such as coronary artery calcification or harder endpoints of cardiovascular disease such as clinical coronary heart disease events.

Keeping these unresolved questions in mind, the findings from Sun et al[7] underscore the importance of preventing or ameliorating cardiovascular risk early in life and may help guide health policies. Early studies suggest that epigenetic aging can be modulated by simple lifestyle interventions, such as diet and exercise.[10] Although the clinical benefits of such modulation remain to be determined, evidence to date raises the intriguing possibility that epigenetic aging can be leveraged as a biomarker to monitor early interventions and promote health across the lifespan.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Zannas was supported by National Heart, Lung, and Blood Institute grant R01HL163031. Dr de Vries has reported that he has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS biological aging, cardiovascular disease risk factors, epigenetic age acceleration, lifespan, subclinical atherosclerosis