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Epigenetic Age Acceleration: A Biological Doomsday Clock for Cardiovascular Disease?

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Epigenetic age seems like a concept pulled from a futuristic science-fiction movie where a drop of blood is fed into a machine, in which an algorithm churns through an accumulation of chemical groups coating a strand of DNA and spits out an individual's true age reflecting a lifetime of experiences and exposures. Remarkably, this fiction moved closer to reality with astute observations that DNA methylation patterns predictably change over time and are highly correlated with age.[1] These observations and the proliferation of high-density methylation microarrays on large sample sizes led to the application of machine-learning approaches to sift through the high-dimensional methylomic data to identify a parsimonious set of informative markers to reconstruct an individual's age; two popular sets were proposed by Horvath[2] and Hannum *et al.*[3] in 2013, although various subsequent adaptations have been developed. These DNA methylation-predicted ages turn out to perform remarkably well; demonstrating very strong correlations with chronological age. While the novelty of using an overly complicated and costly Rube Goldberg machine approach to determine something that only requires a simple question to obtain holds a peculiar appeal, real-world use cases are evident; such as in a forensics scenario where accurately predicting the age of an individual from an unidentified blood or tissue sample clearly has utility.[4] The possibility of cardiovascular health applications arose when the divergence between DNA methylation-predicated age and chronological age, commonly referred to as epigenetic age acceleration, was found to be linked to clinical traits. A positive or accelerated epigenetic age occurs when an individual's DNA methylation-predicted age is older than their chronological age.

Epigenetic age acceleration and cardiovascular disease

In this issue of *Circulation: Genomics and Precision Medicine*, Roetker *et al.* report the association of epigenetic age acceleration with the risk of cardiovascular disease (CVD).[5] The investigators examined epigenetic age acceleration in a large sample of 2543 participants of the Atherosclerosis Risk in Communities (ARIC) study with a mean age of

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57 years at baseline in 1990–1995 and followed for outcomes over a median of 21 years. All participants of this sub-study were African-American, an understudied population for epigenomics and CVD disparities, from the Mississippi and North Carolina study sites. The investigators examined two forms of epigenetic age acceleration in which DNA methylation-predicted age was generated from microarray-based measures of leukocyte-derived DNA methylation at either 71 or 353 cytosine-guanine dinucleotides (CpGs). The two DNA methylation age predictors were moderately correlated with each other (r=0.6) and there was a spread of eight to nine years in epigenetic age acceleration or deceleration across the cohort participants. Incident CVD outcomes, assessed by annual surveillance, hospital record diagnosis codes, and validated by physician review, included probable or definite myocardial infarction, fatal coronary heart disease (CHD) event, peripheral artery disease, heart failure, and CVD mortality. Subclinical atherosclerosis, assessed by ultrasound imaging of carotid intima media thickness (cIMT), was studied in relation to concurrent epigenetic age acceleration measures.

The investigators demonstrated that both epigenetic age acceleration measures are associated with classic CVD risk factors at baseline, such as male sex, smoking, and diabetes. Each of those factors are related with an epigenetic age that is one to two years older than chronological age. At baseline, epigenetic age acceleration is associated with cIMT after adjusting for chronological age, sex, education, health behaviors (smoking, alcohol intake, sports index), body mass index, diabetes, systolic blood pressure, use of antihypertensive medications, total cholesterol, high-density lipoprotein cholesterol, use of cholesterol lowering medications, self-rated health status, cell count, and methylation technical and batch covariates; demonstrating approximately 0.01 mm thicker cIMT per five-year increment in epigenetic age acceleration. Participants were found to be at a 10–20% increased risk for most of the CVD outcomes per each five-year increase in epigenetic age acceleration in similar multivariable-adjusted models. Unsurprisingly, the magnitude of the association with cIMT and incident CVD events is smaller for epigenetic age acceleration than that observed for the same increment in years of chronological age. However, the regression coefficients are closer than what may have originally been expected. For example, the strongest relationship is for fatal CHD events with hazard ratios (HR) per five-year increase in epigenetic age acceleration of 1.17 (95% CI 1.02, 1.33) and 1.22 (95% CI 1.04, 1.44) for the Horvath and Hannum predictors, respectively; which is around half the magnitude as observed for chronological age (HR 1.35 [95% CI 1.15, 1.59]). Despite being assembled from less CpGs (71 vs. 353), the epigenetic age acceleration based on the Hannum markers, which was derived from whole blood samples, is more strongly linked to CVD outcomes than the epigenetic age acceleration based on the Horvath markers, which were derived in multiple cells and tissues; likely due to the current study sample using DNA derived from whole blood leukocytes. While there is no internal or external replication, the findings are consistent with previous reports from meta-analyses of multiple cohorts linking epigenetic age acceleration with all-cause mortality.[6, 7] Results from previous single cohort analyses examining epigenetic age acceleration and CVD outcomes were mixed.[8–10] Further cross-cohort replication and meta-analyses are warranted. Taken together, this report furthers the robustness of the link between epigenetic age acceleration and CVD.

What biological process is epigenetic age measuring?

Epigenetic age is clearly a strong biomarker for aging but it is a mystery as to what age-related biological process it is measuring; it is unknown whether it contributes to CVD pathogenesis or is a non-causal biomarker. At the level of a DNA strand, methylation is binary with either a methylated or unmethylated cytosine residue of a CpG dinucleotide. However, DNA methylation arrays, on which the epigenetic age predictors are based, quantitate continuous methylation as the proportion of methylated CpGs to total CpGs at a given position in the entire amount of DNA in a sample. Therefore, differences in continuous DNA methylation may reflect not only genomic regulatory changes in all or some cell lines in a sample, but also changes in cell proportions and cell state. Epigenetic age acceleration may be capturing these phenomena. Age-related changes in the immune system featuring immunosenescence and chronic low-grade inflammation are linked to CVD,[11] and they may be partly present in cellular changes captured in age-related DNA-methylation differences. In this study, further adjustment for C-reactive protein, a non-specific marker of inflammation, along with renal function in a subgroup analyses did not substantially alter the association between epigenetic age acceleration and CVD outcomes. All models were adjusted for imputed cell counts but residual confounding may still be present that cannot be completely abrogated with computational methods. Similarly, models were adjusted for classic CVD risk factors, such as diabetes, hypertension, and dyslipidemia, but residual confounding due to the length of exposure to these metabolic dysfunctions may be reflected in the aging-related DNA methylation markers and drive part of the association.

Epigenetic age acceleration is surprisingly heritable, with an estimated heritability > 0.3, and therefore likely genetic contributions.[6] An intriguing clue to the underpinnings of epigenetic age acceleration can be obtained from a recent genome-wide association study in almost 10,000 participants identifying associations with SNPs in the *telomerase reverse transcriptase (TERT)* loci.[12] These findings are supported by observations that higher epigenetic age acceleration is associated with shorter telomere length.[13] Whether the genetically-driven component of epigenetic age acceleration, linked to telomerase biology, is driving the association with CVD outcomes is unknown. The authors of the current study attempted to delve into the mechanistic components of the link between CVD and epigenetic age acceleration and broke down the epigenetic age predictors into their single CpG components and tested them in association with CVD outcomes. The strongest link was with differential methylation at a CpG in the *galanin receptor 1(GALR1)* loci. A neuropeptide receptor primarily expressed in the brain and spinal cord, but also present in the heart. The complex connections between all these factors remain to be elucidated.

Doctor! My epigenetic age isn’t looking good. What should I do?

Direct to consumer testing for epigenetic age acceleration is currently available,[14] so it may not be too long before a patient arrives at a doctor’s office seeking advice. However, there are many unanswered questions about epigenetic age acceleration. It is unknown if the phenomena can be prevented, slowed, or reversed; although, lifestyle factors appear promising. Observational data from the Women’s Health Initiative demonstrates that a higher intake of vegetables, fruits and fish is associated with reduced epigenetic age

acceleration at a single time point.[15] In addition, murine models have shown that reduced caloric intake protects from age-related DNA methylation changes.[16] The performance of epigenetic age acceleration to meaningfully improve CVD risk prediction has yet to be formally evaluated but the benefits will likely be modest. More work needs to be done to better understand the clinical applications of DNA methylation. The insurance industry has moved quicker and epigenetic age acceleration may soon be used to predict risk of CVD and mortality to determine insurance premiums.[17]

Conclusions

Roetker and colleagues provide comprehensive evidence of a link between epigenetic age acceleration and CVD outcomes in an African American population from the ARIC study. It is important to recognize that the development of the epigenetic age acceleration metric would not have been possible without open science and data sharing allowing questions to be asked that were never envisioned by the original research project teams. The possibilities to utilize this phenomenon to improve cardiovascular health are tantalizing but many unanswered questions remain; the underlying mechanisms are unknown, the performance as a CVD prediction marker is untested, and the ability to develop and guide interventions based on epigenetic age acceleration to prevent CVD is theoretical. Regardless, the consumer and financial fields have pushed ahead. Significant future research is warranted to translate DNA methylation biomarkers and epigenetic age acceleration measures into effective clinical and public health applications.

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