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Is high dietary quality the real fountain of youth?

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DNA methylation is one of the most studied epigenetic marks related to chronic disease risk. Changes in DNA methylation have been implicated in the pathogenesis of diseases that are largely influenced by dietary quality, including cardiovascular disease and cancer. Recent work suggests that diet can have a major impact on an individual's epigenome. For example, in an epigenome-wide analysis, DNA methylation was correlated with dietary quality measured by both the Mediterranean-style Diet Score (MDS) and the Alternative Healthy Eating Index (AHEI) (1). In this analysis of the causal association between diet quality, changes in DNA methylation, and cardiovascular disease risk, the authors found that dietary quality rather than cardiovascular disease was more likely to contribute to the observed DNA methylation changes. Furthermore, the diet-associated DNA methylation changes were also associated with a higher risk for all-cause mortality.

Other meaningful methods of assessing and interpreting DNA methylation related to health outcomes have been developed, potentially expanding the clinical utility of DNA methylation measurement. Epigenetic clocks, based on DNA methylation at specific sites along the genome, have been created to predict life span and biological aging. The original clocks were developed with algorithms based on DNA methylation to predict age, whereas the second generation of epigenetic clocks also incorporated additional DNA methylation sites that differ by smoking pack years, plasma proteins, and other clinical metrics associated with morbidity and mortality to determine epigenetic age (2). Many of the epigenetic clocks present epigenetic aging in years, so they can be used to determine if the epigenetic age is greater or less than chronological age. Accelerated epigenetic aging, indicating the biological aging is greater than chronological age, has been associated with a broad range of outcomes, including those influenced by dietary quality, such as time to coronary heart disease. The second generation of epigenetic clocks was designed to be sensitive biomarkers for detecting effects of stress and physiologic risk factors associated with changes in the epigenome, making them useful for assessing the effects of lifestyle factors on biological aging.

Two recent studies in the *American Journal of Clinical Nutrition* analyzed associations between diet quality and a variety of epigenetic aging measures (3, 4). Although conceptually similar, the articles assessed the impact of overall diet quality with slightly different outcome measures, which resulted in the tantalizing suggestion that a high-quality diet may have the potential to mitigate the effects of other lifestyle factors associated with epigenetic age acceleration. The first study, by Kim and colleagues (3), evaluated a cohort of non-Hispanic white males and females from the Framingham Heart Study Offspring cohort. Epigenetic age acceleration was assessed using 3 of the second-generation epigenetic clocks to determine *1*) if there was a relation with diet quality assessed by Dietary Approaches to Stop Hypertension Trial (DASH) score and *2*) if epigenetic aging mediates the relation between diet and all-cause mortality. A higher DASH score, representative of higher diet quality, was associated with less epigenetic age acceleration among all 3 of the clocks. Importantly, in sensitivity analyses, the magnitude and direction of associations remained with use of other dietary quality indicators (AHEI and MDS) for all clocks. The associations also remained when controlling for cell types, which is an important consideration because blood cell counts can influence DNA methylation patterns, particularly as immune cell counts shift with aging. These sensitivity analyses strengthen the argument that there is a strong relation between overall dietary quality and markers of epigenetic aging.

Kim and colleagues (3) also evaluated interactive effects of other lifestyle factors, such as physical activity and smoking, with diet quality and epigenetic ageing. Interestingly, the association between diet quality and all-cause mortality was greatest among ever smokers. In other words, the slowing of epigenetic age acceleration among smokers with the highest diet quality was the greatest. However, the second-generation epigenetic clocks, particularly GrimAge (2), were created to be inclusive of surrogate DNA methylation marks of smoking pack years and may be biased to detect differences in sites most affected by smoking. The authors did not detect interactions of diet quality with age, sex, BMI (in kg/m^2), or physical activity. This was somewhat surprising because previous studies have reported associations with BMI and epigenetic age acceleration (5, 6). However, the relation may be more pronounced among those with

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higher BMIs or with longstanding obesity. The mean BMI in Kim and colleagues (3) study ranged from 27 to 29, which may not have been high enough to detect accelerated epigenetic aging in this cross-sectional cohort.

A second related study by Kresovich and colleagues (4) evaluated the relation between multiple dietary indices with first- and second-generation epigenetic clocks among a population of non-Hispanic white females enrolled in the Sister Study. Their analysis confirmed results from the Kim et al. (3) study, in that they also identified an inverse association with all dietary indices and epigenetic aging using second-generation clocks when adjusting for confounders. The mean BMI of participants was 27, and like the study by Kim et al. (3), BMI did not modify the interaction between diet quality and second-generation epigenetic clocks. However, in a stratified analysis of BMI $\geq$30 compared with $<$30, BMI did modify the association between the Healthy Eating Index and Hanuum's first-generation clock, with a stronger inverse relation for those with higher BMI. In contrast to the results by Kim et al. (3), the analysis by Kresovich et al. (4) found that the inverse association with AHEI and adjusted Mediterranean Diet Score (aMed) indices on epigenetic aging was stronger among never smokers and observed a stronger influence of dietary quality on epigenetic aging among participants who did not meet minimal the physical activity recommendations of 2.5 h/wk. This association was most pronounced with the DASH and aMed diet indices and the PhenoAge second-generation clock. The analysis performed by Kim et al. (3) was completed using a composite physical activity score based on intensity and duration of an activity, instead of using the stratified approach based only on activity duration applied by Kresovich et al. (4). Interestingly, previous work by Kresovich et al. (7) found that associations with epigenetic aging and physical activity were diminished after statistical adjustment for BMI and waist circumference. Because both studies evaluated these relations using only a single measure of epigenetic aging, longitudinal studies evaluating change in epigenetic age over time may clarify the true impact of physical activity, diet, and smoking interactions on biological aging.

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