

Growing Old Before Their Time: Measuring Aging

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In this issue of *Pediatrics*, Raffington et al¹ describe an association between early childhood disadvantage and a measure of aging based on DNA methylation. Pediatricians will be intrigued by the concept that a genome-based measure can quantify and perhaps partially explain the well-known link between social equality and remote health effects, including obesity, hypertension, and cardiovascular disease, as well as an easily measured early predictor of whether an initiative to mitigate these morbidities is likely to be successful. Because some of the underlying biological concepts may not be familiar, it will be helpful to discuss DNA methylation and “methylation age.”

The genetic code is embedded in the DNA sequence of the 4 canonical nucleobases: adenine, guanine, thymine, and cytosine. This sequence specifies the messenger RNA that codes proteins, several types of functionally active non-messenger RNAs, and diverse control and structural regions. DNA bases are also subject to chemical modification. The most relevant modification for this discussion is methylation of some cytosines (addition of CH₃) to form 5-methylcytosine.

Methylation of cytosine regulates the rate of RNA transcription and therefore regulates which proteins a cell expresses. During development, patterns of methylation change in a tissue-specific and age-dependent manner.^{2,3} The advent of rapid sequencing makes it simple and inexpensive to analyze the methylation

state of hundreds of thousands to millions of cytosines in a sample of blood cells or saliva, which contain abundant cellular DNA. It has been long known that the extent of DNA methylation in most tissues increases with a person’s chronological age. Moreover, it is possible, by using a variety of statistical techniques, to quantify the link between a person’s chronological age and the extent of DNA methylation at a few hundred cytosines. Several such “methylation clocks” or “epigenetic clocks” are available and in wide use.⁴ Although differing in which cytosines are used, various clocks provide generally comparable results. Finding that a person’s methylation age is greater than their chronological age has been taken as evidence of increased “biological age” and perhaps a tendency to greater future morbidity. Indeed, methylation age is advanced in association with a number of childhood and midlife adversities as well as morbidities such as atherosclerosis, cancer, and obesity.^{4,5}

In their article, Raffington et al¹ test in a cohort of children a relatively new method of age measurement that is designed to represent the pace of aging. Termed DunedinPoAm, it was crafted by comparing the chronological age of ~1000 participants in the New Zealand-based Dunedin Longitudinal Study at ages 26, 32, and 38 years to a group of 18 physiologic measures familiar to pediatricians, including Hemoglobin A1C, BMI, total cholesterol, and cardiovascular fitness.⁶ The changes in these measures between 26



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and 38 years of age were reduced to a composite variable, which was then regressed against DNA methylation at age 38 years. The result is a methylation-based “pace of aging” measure. In adult series, it has been validated to predict functional decline in adults, chronic disease, and mortality, as well as the effect of early-life adversity. However, DunedinPoAm has not been tested before in a group of children.

Raffington et al¹ employ a study of twins (the Texas Twin Study) to examine how measures of family-level disadvantage affect methylation-based pace of aging (eg, household income, parental education, residential instability, etc) and neighborhood-level disadvantage (eg, proportion unemployed or living below the federal poverty threshold, etc). Potential confounders such as puberty, exposure to cigarette smoke, and BMI were considered.

The basic finding is that among white and Hispanic children, greater socioeconomic disadvantage was significantly associated with faster pace of aging as measured by DunedinPoAm ($r = 0.18$). Moreover, adjusting for group differences in family-level and neighborhood-level disadvantages largely accounted for differences in pace of aging between Hispanic and white children. It is reassuring that the measure’s predictive power was robust to confounders such as smoking, body mass, and puberty.

The association between pace of aging and disadvantage is not

surprising because previous methylation clocks have been shown to be sensitive to a variety of early- and midlife adversities.^{4,5} However, the finding that several of these methylation clocks were not associated with either family or neighborhood disparities suggests either that the DunedinPoAm measure is more sensitive to neighborhood and family adversities or that it measures a different sort of organismal response. It is consistent with the suggestion but does not establish that social determinants of health affect risk for disease in part by modifying DNA methylation, thereby altering biological age. If this is the case, then we would predict that DunedinPoAm is correlated with other measures of biological aging, such as mitochondrial function and structure, telomere length attrition, and accumulation of specific cellular proteins.^{7,8} Until this research is available, it is worth remembering that associations with either methylation age or pace of aging and health or longevity may represent the effect of an exposure on both the measure and the outcome of interest rather than a causal pathway that runs from the exposure (low socioeconomic status, adversity) to health outcome (ie, cancer, vascular disease). Although this research applies only to groups or populations of individuals, rather than enables predictions with respect to a specific person, Raffington et al¹ provide a useful conceptual advance to the study of links among adversity, health, and aging.

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