Residential area-based measures were recognized to associate with differential health outcomes at least half a century ago and were linked to socioeconomic distinctions.1,2 Disadvantaged neighborhood of residence is associated with earlier mortality and incident disease,1-3 even when adjusted for other socioeconomic variables.2,3 Health risks differ across neighborhoods based on level of advantage in people of the same race,3 but within disadvantaged areas the health risks tend to be higher for individuals who belong to racial and ethnic minority groups. Quantifying neighborhood racial and economic characteristics is complex. A new report delved into these relationships using novel approaches, including separate metrics for neighborhood racial composition and economic deprivation, and a unique and robust distance-decayed measure for racial composition.4 The investigative team evaluated the connection of both factors with estimates of biological age derived from DNA methylation patterns. In middle-aged and older adults who at baseline were free of cardiovascular disease and resided in six US locales, baseline Census tract was utilized to compute the two neighborhood metrics.4 DNA methylation was tested in blood samples taken 10 years post-baseline and four epigenetic clocks were calculated, allowing for a decade of changes to occur in methylation patterns after baseline exposures.4 The GrimAge methylation clock was associated with greater age acceleration in Black and Hispanic individuals than in White individuals, while the other 3 clocks were not significant.4 The association was strong for neighborhoods with more segregation and more poverty, with particular concerns for non-Hispanic Black participants for whom greater segregation was associated with age acceleration, while for Hispanic participants, greater poverty was associated with accelerated aging.

Although the DNA sequence remains unaffected when epigenetic changes occur, modified DNA methylation affects protein expression and thereby may alter a person’s physiologic condition. DNA methylation patterns can be changed by many factors. For example, gene methylation may be changed by medical treatments and surgery. Bariatric surgery modifies DNA methylation of potentially thousands of genes,5 and those changes may persist for over a year after surgery. Methylation of genes is also influenced by human behavior and by a person’s environment. Methylation patterns can be remodeled by many factors such as smoking, physical activity, diet, infection, and stressors from the childhood environment (eg, lack of loving adult support, malnutrition), adverse living conditions (eg, noise pollution, particulate matter air pollution), and poor interactions with others (eg, emotional or physical abuse). Surprisingly, patterns of methylation are also heritable.5

DNA methylation clocks are measures of biological age that utilize calculations derived from methylation measured at many genetic loci. Names of methylation clocks may be the first author of the original paper (ie, Horvath and Hannum clocks) or, for what are called second-generation clocks, descriptors given by the original developers (ie, PhenoAge and GrimAge). These biological measures are intended to estimate physiological aging rather than linear time-since-birth (ie, chronological age). The Horvath and Hannum clocks are more correlated with chronological age than PhenoAge and GrimAge in prior studies. The clocks are associated with a multitude of endpoints, including risk factors for chronic diseases, disease diagnoses, and mortality.6 Specifically, accelerated biological age is associated with higher body mass index, male sex, alcohol use, smoking, lower socioeconomic status, less education, lower level of physical activity, cardiovascular disease, cancer, poor lung...
function, chronic obstructive pulmonary disease, human immunodeficiency virus infection, diabetes, depression, posttraumatic stress, schizophrenia, and earlier death. Methylation clocks may associate with cognitive dysfunction and impaired ability to learn, among other endpoints.

Studies of neighborhood characteristics are difficult to perform, but the Hicken study was performed well with robust measures of poverty and racial segregation. A few key limitations deserve mention. First, the measurement of methylation clocks was conducted at Exam 5, 10 years after baseline. An assumption is that health changes due to residential racial and economic conditions had occurred after 10 years, but this unknown. To partly alleviate such concerns, the authors examined whether statistical adjustment for baseline covariables (ie, smoking, alcohol, BMI, and count of comorbidities) changed the study findings compared to using those same covariables measured at exam 5. However, it is not clear that changes in those variables are connected to changes in methylation patterns and some such as comorbidities do not go away once diagnosed while methylation can be reversed. Thus, while the 10-year lag from baseline to methylation testing likely allowed enough time for neighborhood characteristics to impact methylation clocks, the data do not rule out the possibility that methylation patterns at exam 5 predated residing in their neighborhood. Future studies should examine longitudinal changes in methylation clocks.

The study also assumed that the baseline neighborhood of residence remained the same 10 years after enrollment. This is not the case for all people enrolled at baseline, and partly is of note since migration in the US may vary by socioeconomic status. Further, some people enrolled at baseline were lost to follow-up or deceased before exam 5 and are not represented. Care should be taken in generalizing the findings outside of people who are at low risk of cardiovascular disease and fit the study selection criteria.

Despite these limitations and that the study cannot demonstrate causality of neighborhood factors driving biological aging, Hicken reports a unique and powerful approach for finding neighborhood factors marking risks of early death and disease. Measurement of racial segregation using spatial clustering methods and separating that from economic deprivation (and education) aid in clarifying the sources of health concerns. This information can guide future mechanistic research regarding causal factors and can direct policy, prevention, and health care efforts. For example, in prior studies, location of residence was connected to risk-associated modifiable behaviors, including smoking, physical activity, stressors, and diet. In one study, prospectively-evaluated 10-year physical activity change scores were lower in neighborhoods that were disadvantaged despite that physical activity is not considered a socioeconomic variable. The choice to engage in physical activity may arise in part from neighborhood characteristics such as ease of or enjoyment of physical activity in a specific neighborhood, or its safety due to exposure to traffic, harassment, or crime.

The measurement of racial and economic factors as effected by Hicken et al, coupled with health trajectory measured by methylation clocks, reveals insights not previously possible. It suggests that living environments and behaviors associated with neighborhoods should be considered in evaluating health trajectory and interventions to modify the trajectory. Differences in basal health and health trajectory exist between individuals based on demographic, anthropometric, dietary, physical activity, psychological, and physiological characteristics that are commonly measured and on sociobehavioral and psychosocial characteristics that are not as frequently considered. While traditional health measures can reveal current health status and be used to project future health, neighborhood of residence, social interactions, environmental exposures, perception of health and health care, and other socioeconomic factors are also important prognostic tools. Considering such information in health evaluations should improve the personalized delivery of care and health guidance, but this rests on understanding each person's needs. When individuals are understood, their real needs become apparent and achieving the healthiest life possible is feasible. Measurement is the first step toward understanding, including measuring neighborhood racial segregation and poverty.