HUMAN AGING

Youthfulness begins in youth

Chronological age fails to capture how the process of aging differs between individuals. Variability in rates of biological aging in youth is related to anatomical and functional differences already visible by midlife. This portends substantially different aging outcomes that have individual- and societal-level implications.

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We all know older people who seem to be much younger than their age — individuals who not only look younger but who have a youthful outlook, intellect and vigor, and who have avoided many age-related diseases. Conversely, there are those less fortunate who appear older than their years and who may have experienced more than their share of disability and illness. Indeed, one of the most well-recognized phenomena of aging is its variability; older people are more different from one another than are younger people, and most biological measurements occur over a wider range in older people[1]. On the other hand, within individuals, variability is lower such that people who are doing better than average for their age on one measure generally do so on multiple measures. This situation can be conceptualized as a discrepancy between chronological age and biological age, the latter reflecting the health status of multiple organ systems in a person. While we think of people at the extremes of this chronological/biological discrepancy as having good or bad fortune in the 'genetic lottery', in fact, we can measure many different factors that may reflect both genetic and environmental origins of biological aging. By measuring the appropriate variables, we can potentially estimate the rate of biological aging, open the door to understanding how aging differs between individuals and potentially predict health outcomes. A number of different biomarkers have been employed to assess biological aging, including DNA methylation[2,3], telomere length[4] or multiple blood measurements of organ system function[5]. A relatively unexplored area is the use of longitudinal measurements that can provide an actual estimate of change in age-related parameters over time. In this issue of *Nature Aging*, Elliott and colleagues[6] following the Dunedin cohort show that longitudinal laboratory measurements of multiple organ systems in youth can model individual rates of biological aging that

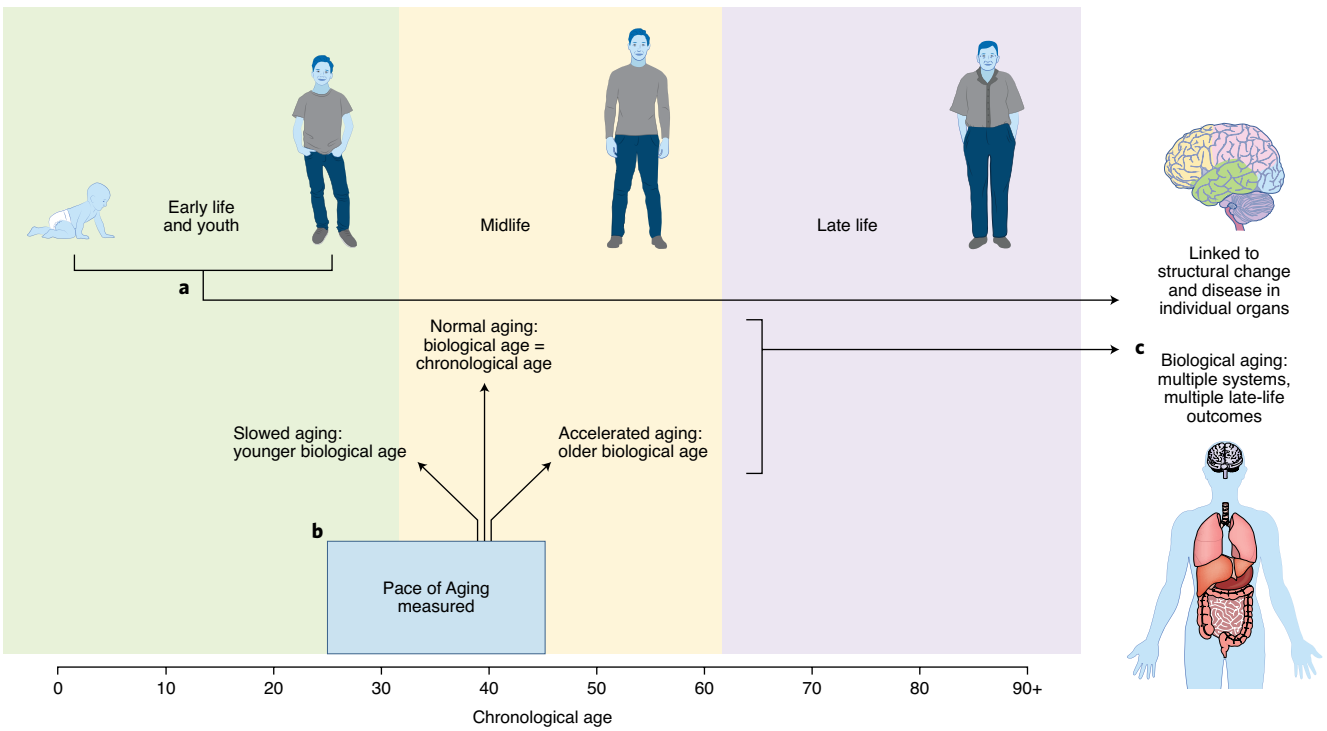

Fig. 1 | The effects of aging are highly variable between individuals and have their origins in early life. a, Events in early life and youth, measured at one time point, have been linked to late-life disease in single organs; for example, the brain. **b**, In the current study, rather than a single organ system measurement at a single time point, investigators used longitudinal biomarker measurements of multiple organ systems to calculate a Pace of Aging from ages 25 to 45. This permitted the calculation of a rate of biological aging that could be compared to individuals' chronological age. **c**, The Pace of Aging measured in midlife shows relationships with multiple organ systems that have implications for many different types of later life outcomes that portend disability or superior health.

are related to a variety of important aging outcomes already visible by middle age.

The Dunedin study initially recruited 1,037 individuals born in Dunedin, New Zealand, over a one-year period from 1972–1973. Participants were followed longitudinally, and beginning at age 26, investigators began collecting biomarkers reflecting a wide range of organ system function. The measures were repeated at ages 32, 38 and 45, allowing them to assess how rates of change, which they called the 'Pace of Aging', predicted outcomes that might have deleterious consequences. They did this by standardizing scores on 19 cardiovascular, metabolic, renal, immune, dental and pulmonary measures, defining individual rates of change on each biomarker and summing annual changes of all biomarkers to define each person's Pace of Aging. This numerical value varied from 0.4 biological years for every chronological year of aging to 2.44 biological years for every chronological year: a sixfold range already by middle age. These Pace of Aging measurements were associated with outcomes measured at the 45-year visit that have important implications for future disability. Those with faster Pace of Aging showed thinner cortex on brain magnetic resonance imaging (MRI) as well as a smaller cortical surface area and more evidence of disease in the white matter, factors which led to a machine-learning estimate of brain age that was older than chronological age. Faster Pace of Aging was also associated with lower intelligence quotient (IQ), which reflected verifiable decline from scores at younger ages along with poorer scores on multiple neuropsychological tests and cognitive ratings by informants familiar with the participants. Measures of potential frailty such as gait, balance, grip strength, visual and auditory perception, and self-rated physical performance were all diminished with faster Pace of Aging. Finally, those with faster Pace of Aging had more negative attitudes towards aging, felt that they appeared older than their age and, in turn, were rated as looking older than their age by others. In a series of follow-up analyses, controlling for potential confounders such as body mass index, smoking, cancer, diabetes and heart disease did not substantially change the associations, nor did results differ by sex.

The study demonstrates how multiple biological processes change early in life and have measurable consequences by midlife that are likely to be important harbingers of later-life disability or superior health. Features that add to the credibility of the study are the longitudinal cohort design, which eliminates the secular effects that are common in cross-sectional studies of aging, as well as a very low rate of attrition. Studies in young people also avoid the problems of survival bias, wherein studies of older people reflect those who have been selected to live to older ages. Importantly, the investigators designed the study so that the outcomes at age 45 did not share measurements with the variables used in deriving the pace of aging. In fact, most of the outcome measures reflected events occurring in the brain and central nervous system. This includes obvious brain measures (brain structure and cognition), likely brain measures (sensory motor function at age 45 probably has a stronger neurological than musculoskeletal component) and affective aspects of behavior (subjective appraisals of age). These outcomes may be particularly salient if they predict later-life cognitive decline and dementia, physical frailty, traumatic injuries and affective disorders (Fig. 1).

While none of the outcome measures in this study bear the unarguable stamp of any specific disease (for example, the brain volume reductions are not necessarily reflective of the preclinical stages of Alzheimer's disease)[7], they are nevertheless suggestive of later conditions that could have important consequences for daily function and mortality. Indeed, one of the interesting points of this study is that without linking to a specific disease, the variability of aging that can be detected by midlife provides evidence for a panoply of later problems that do not necessarily fall in the domain of any single organ system or disease. This strengthens the argument for considering the biological basis of aging as a worthwhile target for intervention. It also points out that individuals differ so widely that the use of chronological age for planning societal-level and individual support services needs improvement in view of the wide variability of aging rates across the population.

The idea that early life events have profound consequences for later-life neural function is consistent with an increasing number of cohort studies that have used innovative methods to link these life stages. The challenges of empirically relating childhood exposures to aging outcomes are obvious but have been addressed by studies that have followed or reassembled cohorts established in youth for evaluation in mid- or late-life. The Scottish birth cohort studies, for example, have been able to show how estimates of IQ at age 11 explain much of the association between IQ and brain size (measured with MRI) in the eighth decade[8]. The Insight 46 study and the Vietnam Era Twin Study of Aging have both shown similar relationships between cognition measured in youth and cognition in late-middle-age and older[9,10]. Another way of surmounting the necessity of lifelong longitudinal studies is a cohort-sequential design that makes use of multiple cohorts studied over different time periods of the lifespan. This approach has shown that early life exposures — which include birth weight, parental education and genetics — affect brain structure such that those with larger cortex maintain their advantage over their peers throughout life[11].

The work reported by Elliott et al., however, is not simply a matter of predicting an outcome in midlife, or later life, based on an early life measurement. The authors report a measure that is not static but which dynamically reflects change. The fact that the Pace of Aging is fundamentally a slope means that if change is linear, which was the case up to age 45, individuals with faster biological aging will show even greater differences from their more slowly aging peers over time. In other words, aging is a process, not a single event, and we must make longitudinal measurements in order to understand it. If a single early life exposure is related to a poor late-life outcome, it could be relatively straightforward to intervene to avoid this outcome. But as something that begins in youth, aging calls out for an intervention that slows the fundamental biological process, which would have implications for numerous later-life outcomes. It is a long road from intervening to prevent a disease to intervening to slow the rate of aging, but empirically measuring the rate of aging is the first step. ❐

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Published online: 15 March 2021
https://doi.org/10.1038/s43587-021-00048-0

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Competing interests

W.J.J. has served as a consultant to Genentech, Roche, Biogen and Bioclinica.