## ABSTRACT

U.S. life expectancy has stagnated and even decreased in some years since 2010. “Deaths of despair” concentrated among White men in young and middle adulthood were identified as a driver of early declines, with more recent evidence showing rising mortality among Black men from these same causes. The impact of the causes of these excess deaths on health trajectories in still-living members of the population remains unknown. Novel measures of biological aging may be well-suited to early population health monitoring, providing readouts of aging-related physiological integrity decades before the onset of disease and disability. We analyzed data from 29,487 participants in the 1999-2018 waves of continuous NHANES to evaluate population aging trajectories in the United States over the first two decades of the 21st century. Biological aging was quantified using the PhenoAge algorithm, with biological-age advancements calculated as the difference between PhenoAge and chronological age. We conducted age-period-cohort (APC) analysis using Bayesian Hierarchical APC models. Mean biological-age advancement rose over the study period 1999-2018 across all race-sex subgroups, with population aging trajectories reverting back to early-1990s levels by 2018. Formal APC decomposition revealed significant period effects across all strata of race and sex, but no significant cohort effects. Our findings suggest that greater attention to the non-fatal impacts of the Great Recession and opioid epidemic may be warranted, especially among minoritized population groups who may experience substantial but non-fatal health decrements stemming from these exposures.

## INTRODUCTION

**American exceptionalism in life expectancy.** The 20th century was characterized by rapid, global increases in human life expectancy (1,2). In the United States and other economically developed countries, early gains were the result of medical advances and improvements in sanitation, while gains in the latter half of the century were driven by improved survival among people with chronic disease. However, these hard-won gains in population health and healthy aging appear to be eroding in the United States, raising alarms among politicians, policymakers, and the lay public alike (3–6). U.S. life expectancy has stagnated since 2010 (7–9). This observation represents a dubious form of American exceptionalism: before the COVID-19 pandemic, life expectancy continued to increase over this same period in the vast majority of high-GDP countries (10).

Several drivers of pre-pandemic decreases in life expectancy have been identified, including rising young adult and midlife mortality attributable to “deaths of despair” in the wake of the opioid epidemic and Great Recession – i.e., suicide, overdose, and alcohol-related liver disease (7,9). While life expectancy declines were not observed until 2014, mortality attributable to these causes was rising as early as the turn of the century- though masked by large reductions in cardiovascular, cancer, and HIV mortality over the same period (7,11). And while all countries experienced precipitous declines in life expectancy in the wake of the global coronavirus pandemic, early evidence suggests that post-pandemic life expectancy trajectories are recovering more slowly in the United States relative to its peers (10,12) – potentially indicating greater underlying vulnerability to adverse health events.

**The challenge of interpreting life expectancy trends in relation to population health status.**Life expectancy is a commonly-used measure in public health with origins in the field of demography (13). For a given birth cohort, life expectancy at birth represents the average number of years one would expect to live, based on the age-specific mortality rates observed in the population during the time interval that cohort was born (14,15). As a cross-sectional summary of age-specific mortality risk, life expectancy thus tells us whether people in a defined population are dying earlier or later compared to past periods. This is useful for within- and cross-population comparisons, with life expectancy consistently demonstrating expected social gradients in health (e.g., educational attainment, social class, racialized group membership, etc.) (7,16–18). Longitudinal analyses and subgroup comparisons thus represent an important indicator of demographic change.

However, life expectancy also has important limitations as an indicator of population health. First, and perhaps most importantly, life expectancy is a measure of mortality: it measures the age at which people die, rather than the health status of living persons (14). When life expectancy is used to describe the health state of living populations, a strong but potentially fallacious assumption is often made: that mortality risk translates neatly to decrements in health status among those still living. This may not be true if the groups at greatest risk of dying are not those who experience the greatest decline in health status among those still living. Measures are therefore needed which provide direct, rather than proxy, measurements of health status. Second, life expectancy cannot provide information about the effects of harmful exposures at timescales appropriate for intervention. Knowing the population groups at greatest risk of dying today does not tell us whether those same groups are at highest risk of disease and disability in the future. Measures are needed that can evaluate the health trajectories of *living* individuals, at younger ages and before the onset of disease and disability (19,20). Finally, life expectancy does not account for the changing meaning of chronological age over time. As noted in the pioneering work of Sanderson and Scherbov, increases in lifespan are often accompanied by corresponding increases in healthspan (21). Accurate measurement of population health trajectories depends on whether measures of population health can account for secular trends in in age-related health status over time.

Early observations of stagnating life expectancy were driven by an increase in “despair”-driven mortality among White men in young and middle adulthood (7,9). More recently, mortality from drug overdose has also increased among non-Hispanic Black and Native American men, surpassing rates observed among White men in the first decade of the 21st century and suggesting broader population impacts than initially observed (22–24). How the causes of these excess deaths impact health trajectories in these and other population groups, including women and birth cohorts in other life course stages, remains unknown. On the one hand, recently observed “deaths of despair” may represent the tip of an iceberg signaling broad shifts in morbidity and mortality. The causes of these deaths, including mental health problems and substance use disorders, could be compromising long-term health trajectories more broadly- even if fatal impacts are concentrated among specific population groups due to structural and behavioral factors (25,26). Alternatively, the greatest impacts of these exposures might be relatively isolated, with White men experiencing a disproportionately high share of both morbidity and mortality. Because life expectancy relies on observing the occurrence and timing of death, it cannot provide insight into the non-fatal impacts of social and environmental conditions driving increased deaths of despair (15,21). If these impacts are equally distributed across the population, then broad-based policies and interventions will be most effective; if impacts are limited to specific age or demographic groups, then targeted interventions will be most appropriate. Measures which can evaluate health trajectories across a wide range of birth cohorts are needed to identify the populations at greatest risk for future disease and disability.

**Biological aging as an early indicator of population health trends.** A growing body of evidence indicates that biological aging measures may be well-suited to monitoring population aging trajectories, while addressing several of limitations of life expectancy measures. Biological aging is a construct first introduced by the fields of geroscience and aging biology, and describes the accumulation of physiological damage across multiple body systems that occurs with advancing chronological age (27,28). Hallmarks of this process, as identified by López-Otín and colleagues, include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (29). These decrements originate at the molecular level and are observable across multiple body systems, mediating the eventual manifestations of age-related disease and disability (19,28). Quantifications of biological aging are being developed in the nascent field of geroscience to assess these pre-clinical decrements as a modifiable risk factor for aging-related health outcomes (20,30). To the extent that measures of biological aging reflect latent decrements in physiological integrity that result from the accumulation of compounding health risks, they provide an appropriate means through which to evaluate contemporary trends in population health and inform timely, actionable health policy.

There are multiple mechanisms through which social and environmental factors might impact biological aging trajectories. First, exposure to social stressors has been shown to trigger endogenous processes that result in damage to cardiovascular and metabolic health. McEwen and colleagues first introduced the concept of allostatic load in 1998: the overstimulation of neural, neuroendocrine and neuroendocrine-immune systems resulting from frequent and sustained exposure to stress (31). Geronimus and colleagues then applied this concept in their research on “weathering”, demonstrating clear racial disparities in allostatic load- a measure of oxidative stress-related aging processes (31–34). Since then, additional research has continued to elaborate associations between psychosocial stress and accelerated aging (35–38). Second, aging-related damage may occur as a result of exogenous exposure to environmental toxicants and constraints that induce adverse health behaviors, including air pollution, socioeconomic status, and neighborhood-level factors (39–42).

Recently-developed biological-aging algorithms are responsive to a wide range of these exposures (43–46), and demonstrate several additional properties well-suited to the evaluation of population health trajectories. For example, many of these measures are sensitive to a range of social and environmental exposures, predictive of morbidity and mortality in diverse populations, and can identify pre-clinical health risk as early as young adulthood; several of these measures use data available from routine blood chemistry tests, which are increasingly collected in large-scale population health surveys (38,44,45,47–54). While there is no gold standard of biological aging (47,55), the most widely-adopted measures to date use machine learning methods to integrate information across multiple clinical parameters collected from blood-chemistry and DNA-methylation data (47,55–58). Machine-learning methods are used to train these parameters on some aging-related outcome (e.g., chronological age, mortality risk, longitudinal rate of physiological decline) in a reference sample, after which they can be applied as outcome variables in new datasets to test hypotheses.

**Study objective.** At a population level, we might expect that – just as historical increases in life expectancy have been mediated through gains in healthspan and decelerated aging (19,59,60) – decreases in life expectancy signal broader health decrements related to aging-related physiological decline (61). To explore the extent to which the causes of pre-pandemic declines in U.S. life expectancy also impacted underlying health trajectories across population groups, we analyzed national trends in population biological aging over the first two decades of the 21st century using data from the continuous NHANES (1999-2018).

A previous study observed changes in population aging between the NHANES III (1988-1994) and 2007-2010 continuous NHANES cohorts (60). We extend this work in two key ways. First, we extend the period over which population aging trends are analyzed, using data spanning the first two decades of the 21st century (1999-2018). This allows for more granular observation of population aging trajectories over the period when U.S. life expectancy began to stagnate and/or decrease. Second, we investigate the extent to which time trends in biological aging were attributable to age, period, and cohort effects using a formal age-period-cohort (APC) decomposition method. By evaluating the extent to which these patterns diverged by racialized group membership, we can determine whether accelerated biological aging trajectories are concentrated in the demographic groups and birth cohorts with the highest mortality risk. Together with existing data on life expectancy trends, findings from this study can inform the development of appropriately targeted and timely public health interventions.

## METHODS

**Sample.** Data were drawn from the National Health and Nutrition Examination Surveys (NHANES), a collection of nationally-representative, cross-sectional health surveys of the noninstitutionalized civilian U.S. population conducted since the 1960s and continuing through the present day. Survey procedures have previously been described in detail (62–67). Briefly, the aim of NHANES is to collect information about the distribution of major diseases affecting the U.S. population, as well as risk factors for those diseases. NHANES interviews include a survey component, a physical exam, and for a subset of participants, the collection of biospecimens through a range of laboratory tests performed in Mobile Examination Centers (MEC). We used data from participants ages 20-80 in NHANES III (fielded 1988-1994) and the 1999-2018 waves of continuous NHANES (fielded biennially) who provided blood samples during the MEC exam and for whom measures of biological aging could be calculated. NHANES III data were used as the reference sample on whom biological aging algorithms were trained, while continuous NHANES data were used as the primary analytic sample.

**Biological aging.** Biological aging is a construct which first originated from the fields of geroscience and aging biology, describing the accumulation of physiological damage across multiple body systems that occurs with advancing chronological age (27,28). The term biological aging is used in contrast to the related but distinct concept of "chronological age," which describes the raw passage of time since birth. While there is no gold standard of biological aging (47,55), the most widely-adopted measures to date use machine learning methods to integrate information across multiple clinical parameters collected from blood-chemistry and DNA-methylation data (47,55–58). Algorithms incorporating these parameters are first trained on some aging-related outcome (e.g., chronological age, mortality risk, longitudinal rate of physiological decline). They can then be applied in new cohorts: “biological age” is assigned as the chronological age at which an individual’s predicted value on some aging-related parameter is approximately normal in the original reference sample on which the algorithm was trained. These measures have been shown in our own work and that of other investigators to be sensitive to a range of social and environmental exposures, to predict morbidity and mortality in diverse populations, and have received substantial attention in the research literature (38,44,45,47–52). Importantly, comparative studies show clinical-lab-based measures of biological age to be equal or stronger predictors of aging-related health deficits and mortality as compared with alternative approaches, such as DNA methylation clocks (47).

The primary measure of biological aging used in this analysis was biological-age advancement, as measured using the blood-chemistry PhenoAge algorithm (48). Following this method, predicted biological age values represent the age at which a participant’s physiology-predicted mortality risk would be approximately normal in the reference sample in whom the data were originally trained. We followed the method originally proposed by Levine and colleagues to train the PhenoAge algorithm in our sample (48). We first defined the universe of available biomarkers collected in all waves of NHANES III and continuous NHANES. We assessed potential batch effects in biomarker values across measurement waves and corrected for these effects for three biomarkers: alkaline phosphatase, albumin, and red cell distribution width. Second, we selected a subset of these biomarkers as predictors for the PhenoAge algorithm by running an elastic net regression model to identify parameters most strongly associated with mortality risk. The 12 biomarkers selected using elastic net regression were: albumin, alkaline phosphatase, creatinine, glucose, uric acid, HbA1c, lymphocyte %, mean cell volume, red cell distribution width, white blood cell count, systolic BP, and pulse. PhenoAge values were then projected into the analytic sample of continuous NHANES participants using the *BioAge* package (27) in the RStudio Integrated Development Environment (IDE) v2023.06.0.421 (68). Biological-age advancement was defined as the difference between PhenoAge and chronological age (e.g., an individual with a PhenoAge of 65 and a chronological age of 60 would have a biological-age advancement, or accelerated aging, of 5 years). Details regarding the development of biological aging measures for this analysis are available in the **Methods Supplement**.

**Age-Period-Cohort (APC) analysis.** Changes in population health indicators over time may reflect one or more distinct phenomena, formally described by the age-period-cohort (APC) framework in life course epidemiology (69). *Age* effects reflect changes in disease prevalence attributable to changes in the age structure of the population. If certain health outcomes are concentrated towards the end of life (or at any other developmental stage), then the prevalence of these outcomes will increase as the proportion of aged persons in a population increases. *Period* effects describe changes in disease prevalence attributable to exposures that affect different age bands relatively uniformly. Finally, *cohort* effects result when a time-bounded exposure affects one birth cohort to a greater extent than others. These mechanisms are not mutually exclusive: age, period, and cohort effects may all be operative at any given time. Identifying age, period, and cohort effects is of public health importance as the policy implications of observing period and cohort effects are markedly different: the former requires broad, population-level intervention, while the latter requires targeted interventions in high-risk populations.

The classical APC identification problem arises from the perfect linear dependency of age, period, and cohort; several methods have been developed to circumvent this issue (70–72). Here, we followed a general approach to APC analysis as outlined by Yang and Land (70). We first identified potential age, period, and cohort effects by identifying non-linearities in two-dimensional age-by-period, age-by-cohort, and period-by-cohort graphs. We then compared goodness-of-fit statistics for a fully specified three-factor model against all possible one-factor and two-factor generalized linear models: three models testing age, period, and cohort effects separately (, where ), and three models testing each possible pair of the three effects (, where ).

We used Bayesian Hierarchical Age-Period Cohort (BHAPC) models to implement three-factor decomposition of age, period, and cohort effects while accounting for survey weights. In cases where individual-level cross-sectional data are available, Yang and Land recommend the use of hierarchical models, where individual (level-1) age effects are nested within higher-level (level-2) period and cohort effects. This technique has previously been described as being compatible with Ryder’s sociological view of age, period, and cohort effects, whereby individuals’ lives as being shaped by their environments, including the constraints and influences of historical time and cohort membership (71,73). Because traditional multilevel models failed to converge under our sample weighting strategy (described below), we fitted Bayesian hierarchical models using weakly informative priors to achieve model convergence (74). Comparison of successfully converged traditional multilevel models with Bayesian multilevel models yielded virtually identical results. All Bayesian models were fitted using the *rstanarm* package (75) in the RStudio Integrated Development Environment (IDE) v1.3.1073 (68). We tested the level of uncertainty around our estimates using 90% credible intervals.

**Evaluating disparities in population aging trajectories.** Guidelines for best practice in APC models suggest constructing separate models for different population groups, rather than including interaction terms within a larger model (72). We therefore repeated all analyses separately by race-sex strata to identify differences in population aging trajectories by race and sex.

**Sampling weights.** NHANES employs a multistage probability sampling design across several domains of key demographic characteristics (e.g., age, race, sex) to select survey participants that can be weighted to provide population-representative estimates of the U.S. civilian non-institutionalized population (65–67,76,77). There are several sampling weights provided in each wave, corresponding to different survey subsamples; separate weights are calculated for the in-home interview, the mobile examination, and for special components such as the environmental chemicals subsample. Weights are constructed based on selection probabilities and non-response rates, with post-stratification adjustment to the entire U.S. population. We used Mobile Examination Center (MEC) subsample weights provided by NHANES to generate population-representative effect-size estimates. The weights account for sampling probabilities as well as potential non-representativeness introduced by survey non-response, and have been used in previous applications of APC approaches in this sample (78,79). Sampling strata and clusters were included as random effects and log-transformations of the sampling weights were included as fixed effects in APC analysis (80–82).

**Sensitivity analysis: measurement of biological aging.** As previously described, different biological aging algorithms are trained on different aging-related constructs using different statistical approaches. We therefore repeated our analyses using an alternative measure of biological aging, Homeostatic Dysregulation (52). Rather than training biomarkers on mortality prediction, as with the PhenoAge method, the Homeostatic Dysregulation measure quantifies an individual’s deviation (as measured using Mahalanobis distance) from the biomarker profile of a young, healthy reference cohort. Consistency of findings across different algorithms builds confidence in primary study findings.

Second, we tested whether APC effects identified in our primary analysis were robust to specification using the full set of biomarkers used by Levine and colleagues in the original PhenoAge measure, that were also available in all waves of NHANES (i.e., albumin, log creatinine, HbA1c, lymphocyte %, mean cell volume, red cell distribution width, log alkaline phosphatase, white blood cell count). The biomarkers used in our analysis were similar to those originally used by Levine and colleagues in the development of the PhenoAge algorithm (48): both measures included albumin, HbA1c, lymphocyte %, mean cell volume, red cell distribution width, white blood cell count, creatinine, and alkaline phosphatase. Our measure also included glucose, uric acid, systolic BP, and pulse, which were not present in the original PhenoAge algorithm. The original PhenoAge algorithm also included a measure of C-reactive protein; we were not able to include this biomarker in our analysis because it was not measured in the 2007 and 2009 waves of continuous NHANES. However, two-dimensional graphical analysis of age, period, and cohort trends using available data indicated that PhenoAge specifications using the biomarker set originally used by Levine and colleagues were similar regardless of the inclusion of the C-reactive protein biomarker.

**Sensitivity analysis: alternative approaches to APC analysis.** We further tested the robustness of study findings to alternative specifications of our age-period-cohort model. First, we employed two alternative methods of age-period-cohort decomposition: the Intrinsic Estimator method and the Median Polish procedure. Unlike the HAPC approach, both methods rely on the use of aggregate data arranged in a two-dimensional age × period matrix. Sampling weights were therefore applied by calculating weighted means for each cell in the age × period matrix. The Intrinsic Estimator is a widely used application of constrained generalized linear models that minimizes identification assumptions (83). Generally, constrained models solve for the equation , where represents a vector of age brackets ­, represents a vector of time periods , and represents a vector of birth cohorts . To address the APC identification problem, at least two parameters within the same vector are set to be equal (e.g., ). The Intrinsic Estimator provides a data-driven solution by identifying the equality constraints that have the least influence on model estimates. The Median Polish procedure, conversely, defines a cohort effect as the interaction (i.e., departure from additivity) of age and period effects (84). In the first phase of the procedure, the median values of each row and column are iteratively subtracted from each cell of the contingency table, until they are approximately equal to zero. The number of iterations needed for the row and column medians to approach zero varies. Finally, estimates of the overall cohort effect are obtained by running a linear regression of the form , where represents the residuals in a given cell identified by the intersection of age group and period , and represents an indicator variable for membership in cohort .

Different approaches to APC identification have different target estimands. These result in different interpretation of cohort effects, as has been discussed in prior literature (71). Briefly, constrained coefficient approaches, including the Intrinsic Estimator, treat cohort effects as the sum of all exposure impacts unique to and shared by a particular birth cohort, independent of (i.e., controlling for) period and age effects. Separately, hierarchical models treat cohort (and period) effects as environmental, group-level factors exerting macro-level impacts on individual lives. Finally, the Median Polish procedure treats cohort effects as age-specific period effects- that is, the departure of additivity from age and period effects together. We therefore conducted comparative analyses using different APC approaches, with the understanding that divergence does not indicate misspecification of any given model. Finally, we repeated analysis using our original BHAPC specification, treating age as a factor variable as in the IE and MP approaches to facilitate comparison across models.

## RESULTS

We analyzed data from 28,991 participants in the 1999-2018 waves of continuous NHANES who provided blood samples during the Mobile Examination Center (MEC) exam and for whom biological aging measures could be calculated. The sample was 49% male and 70% White; mean age at time of survey completion was 50 years (SD=18.2). Overall, participants in continuous NHANES were biologically younger than participants in the NHANES III reference sample conducted from 1988-1994 (PhenoAge advancement mean=-3.1, SD=5.3). Chronological age was highly correlated with PhenoAge (r=0.96), but only weakly correlated with PhenoAge advancement (r=0.09), indicating that effects observed were unlikely to be the artefact of changes in the chronological-age distribution of the population over the study period. Full participant characteristics are reported in **Table 1**; cell-sizes for age-by-period contingency tables are reported in the full sample and by race and sex in **Supplemental Tables A1-A5**.

These findings are partially consistent with overall findings from Levine and colleagues, who reported slower biological aging trajectories in the United States in 2007-2010 relative to the early 1990s, using the Klemera-Doubal Biological Age measure (60). However, we found that mean biological-age advancement rose from 1999-2018, approaching NHANES III levels towards the end of the study period (**Figure 1**). Population aging trajectories appeared to be improving over the 1990s, with biological-age advancement values reaching their lowest point during the 1999-2002 measurement wave. Then, population aging trajectories appeared to reverse, reverting back to early-1990s levels between 2012 and 2018. These trends were observable across all race-sex subgroups.

Preliminary analysis of age, period, and cohort effects was assessed through graphical analysis and comparison of parametric one-, two-, and three-factor models. Graphical analysis revealed weak non-linearity in age effects by measurement wave, with more recent birth cohorts evidencing slightly more advanced biological aging than earlier birth cohorts at the same chronological age (**Figure 2**). This effect was observable in all race-sex strata, though somewhat more pronounced among White participants. In formal comparison of parametric one-, two-, and three-factor models, the fully-specified three-factor model appeared to fit the data somewhat better than both two-factor models (AC model AIC=85,370; AP model AIC=85,324; APC model AIC=80,482 (**Supplemental Table A6**). Because graphical analysis and preliminary model comparison yielded somewhat ambiguous evidence of cohort effects, we fitted fully specified three-factor models to explore each of these effects and evaluate potential differences in age, period, and cohort effects by race and sex.

*Age effects.* Assessment of age effects independent of period and cohort revealed small but significant increases in biological-age advancement alongside chronological age. Comparison of age effects across strata of race and sex also revealed expected social gradients: women evidenced less-advanced biological aging than men, and White participants similarly evidenced less-advanced biological aging than Black participants across the age range of our sample. Observing these social gradients within age effects, rather than period or cohort effects, indicates the consistency of social gradients across all birth cohorts and measurement waves included in this analysis.

*Period effects.* Significant increases in biological aging were observed across all strata of race and sex over the study period. Effect-sizes were most negative, indicating slower aging trajectories, in the earliest waves of measurement (1999-2002, race-sex strata ES range=[-0.14,-0.09]). Conversely, effect-sizes were the largest, indicating faster biological aging, in the latest waves (2015-2018, race-sex strata ES range=[0.10,0.21]). Period effects in biological aging increased from 2003-2007 and consistently from 2011-2018, but dipped between 2007-2011. Trends were consistent across strata of race and sex.

*Cohort effects.* No sustained cohort effects were observed in our analysis, although greater variation in biological-age advancement across cohorts was observed among White women and Black men relative to White men and Black women. The time trends in biological aging observed in our analysis were thus largely attributable to broad period effects rather than concentrated effects within a specific population group or set of birth cohorts. Coefficients of the fully specified three-factor APC model, including age, period, and cohort effects, are reported in **Table 2** and plotted in **Figure 3**.

*Sensitivity analysis: Alternative APC model specifications.*Results of APC decomposition using Intrinsic Estimator (IE) and Median Polish (MP) approaches are not directly comparable to the Bayesian HAPC specification. First, both the IE and MP fit age as a dummy variable, while our primary BHAPC modelled age as a linear and quadratic term. Second, comparisons across categories of race and sex are somewhat more limited in IE and MP approaches, as all effects are zero-anchored to a reference category within the stratified model. However, visual comparison of age, period, and cohort trends over time revealed some commonalities: across all models, significant increases in biological aging were observed after 2007, with limited evidence of cohort effects in the full population or any race-sex stratum. Full results of the IE and MP specification are available in **Supplemental Tables and Figures B1 & B2.** Results of BHAPC analysis specifying age as a factor variable yielded similar results to our primary analysis; results are available in **Supplemental Table and Figure B3**.

*Sensitivity analysis: Alternative measures of biological aging.*PhenoAge was moderately correlated with an alternative measure of biological aging, Homeostatic Dysregulation (r=0.52, **Methods Supplement**).Homeostatic Dysregulation. In contrast to PhenoAge advancement, which decreased from NHANES III to the early waves of continuous NHANES, Homeostatic Dysregulation appeared to increase in the entire population from 1990 to 1999, with continued increases among Black Americans and levelling off among White Americans thereafter (**Supplemental Figure A5**). Results of comparative analysis using alternative APC modelling approaches yielded broadly similar directional patterning, although the relative magnitude of period and cohort effects differed (**Supplemental Table and Figure B4**). Expected age patterning by race and sex were again evident and effect-sizes were comparable. Period effects were attenuated and did not reach statistical significance, likely because time trends in biological aging were less evident overall using the Homeostatic Dysregulation measure. Cohort effects suggested of more advanced biological aging among the 1963-1974 birth cohorts in White women. While this trend was also observable in analysis of the primary PhenoAge measure, the coefficients did not have credible intervals appreciably different from zero. Results of analysis using alternative specifications of the PhenoAge variable (calculating biological-age advancement using an alternate set of biomarkers based on Levine’s original algorithm, and using residualized-change scores) yielded similar results to our primary analysis, although the latter also evidenced cohort effects among White women in mid-century birth cohorts. Full results are reported in **Supplemental Tables and Figure B5 & B6**.

## DISCUSSION

We used repeated cross-sectional survey data from the continuous NHANES (1999-2018) to assess age, period, and cohort trends in biological aging in the US population over the first two decades of the 21st century. Overall, participants in continuous NHANES were biologically younger than participants in the NHANES III training sample (1988-1994). This was consistent with overall findings from Levine and colleagues, who reported lower biological age in more recent periods using continuous NHANES data from 2007-2010 using the Klemera-Doubal Biological Age measure (60). However, mean biological-age advancement rose over the study period 1999-2018 across all race-sex subgroups.

Formal age-period-cohort (APC) decomposition methods were implemented to further explore population trends in biological aging over the study period. The goal of APC analysis is to identify the extent to which age, period, and cohort independently affect time trends in some outcome of interest, by making assumptions which circumvent the perfect linear dependency between the three effects. We used a Bayesian Hierarchical (BHAPC) approach, modelling age as an individual-level effect nest within contextual period and cohort variables.

We observed expected social gradients across the entire age range of our sample, independent of birth cohort and measurement wave: women evidenced less advanced biological aging than men, and White participants evidenced less advanced biological aging than Black participants. Consistent with Gompertz expectations of accelerating senescence with advancing age, we also saw small increases in biological-age advancement alongside chronological age. Following these observations, we identified significant period increases in biological aging over the study period, with increases from 2003-2007 and from 2011-onwards. Our results suggest that while population aging trajectories in the United States slowed between the early and late 1990s, we are now observing a reversal of these gains – especially in the second decade of the 21st century. Limited evidence of cohort effects was observed. Overall, findings were robust to sensitivity analyses that varied the algorithms used to calculate biological age, biomarker composition of biological age algorithms, and methods of APC decomposition, with the exception that 1) analysis using the Homeostatic Dysregulation measure of biological age showed attenuated period effects, and 2) analysis using the Homeostatic Dysregulation measure as well as an alternative PhenoAge specification (using the original set of Levine biomarkers) suggested small cohort effects among White women born in the late 1960s and early 1970s.

Our findings contrast with recent cohort trends evidencing higher mortality among White and Black American men in midlife and young adulthood (85,86). Instead, our analysis of biological aging trajectories suggests that the U.S. population is aging more rapidly overall in the second decade of the 21st century, across dimensions of race, sex, and age. One interpretation of these findings is that the causes underlying deaths of despair among White men in young and middle adulthood may have wide-reaching impacts on population health, across dimensions of race and sex. These increases could be attributable to broad, documented psychosocial stress in the aftermath of the Great Recession, as well as substance-use-related morbidity as the opioid epidemic began to accelerate starting in 2010 and continuing through the present day (87–91). Our results could also explain underlying vulnerabilities that would coincide with poorer population health outcomes relative to other high-GDP countries, including U.S.-specific stagnation in life expectancy trends and slower recovery of health trajectories after the COVID-19 pandemic. For example, the Great Recession is hypothesized to have had disproportionate health impacts on the American population relative to their European counterparts, partly due to stronger safety nets which buffered the worst impacts in those countries (92). The opioid epidemic is almost entirely confined to the American context, driven by both the overprescription of legal pain medication and associated increases in the use of heroin use and illicit synthetic opioids (93,94).

Our findings have implications for future research. First, greater attention to the non-fatal impacts of the Great Recession and opioid epidemic is warranted – especially among minoritized population groups who may experience substantial but non-fatal health decrements stemming from these exposures. Second, research is needed to evaluate the extent to which period trends in population aging are attributable to changes in the distribution of social and environmental stressors over time – particularly those driving increases in mortality in the late 2000s – as well as the extent to which these factors contribute to the persistence of racial disparities in healthy aging over time. Finally, comparisons using data from other high-GDP countries might be used to assess differences in aging trajectories attributable to different social policy environments over this time period.

We acknowledge limitations. There is no gold standard measure of biological aging (55). Our results observing period increases in biological aging could be specific to the measures we analyzed. However, we observed similar social gradients and directionally consistent estimates of APC effects using an alternative measure of biological aging, Homeostatic Dysregulation. Differences in the relative magnitude of period and cohort effects may be attributable to lower sensitivity of the Homeostatic Dysregulation measure to changes in biological aging over time, the relative weighting of individual biomarkers within predictive algorithms, or to differences in the outcomes on which the algorithms are trained. Comparative analysis using other biological substrates (e.g., DNA methylation), once made available, will provide additional insight on the interpretation of these findings. We used cross-sectional panel data from 10 waves of the continuous NHANES; small cell-sizes in some race-sex strata were found at the right tail of the chronological age distribution (smallest cell n=8). This was the result of data on the youngest and oldest birth cohorts being available only in the first or last waves of data collection. We employed a Bayesian multilevel modelling approach in order to maximize the use of available data in our sample, and modelled age as a continuous term. However, repeated analysis using alternative methods relying on aggregate date (e.g. the Intrinsic Estimator and Median Polish procedure), and specifying age as a factor variable, yielded similar results. Finally, APC decomposition methods are fundamentally descriptive: they cannot identify the drivers of observed age, period, and cohort trends, nor of observed disparities in biological aging. Further research is needed to assess drivers of potential age and period changes in biological aging, and the impact of these drivers on observed disparities in healthy aging.

Within the bounds of these limitations, this study represents a proof-of-concept application of biological aging measures to the study of population health. Results of analysis using these measures complement traditional indicators of population health and healthy aging, like life expectancy, by providing direct measures of health status in living people. To the extent that latent biological processes of aging drive disease and disability in later life, collection of biological information to measure population aging outcomes may allow for earlier readouts of long-term population health impacts, decades before the onset and disability. This approach may ultimately prove essential to evaluating the long-term consequences of the COVID-19 pandemic.

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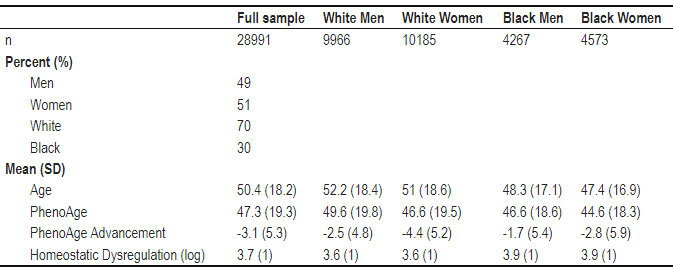
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## Tables and Figures

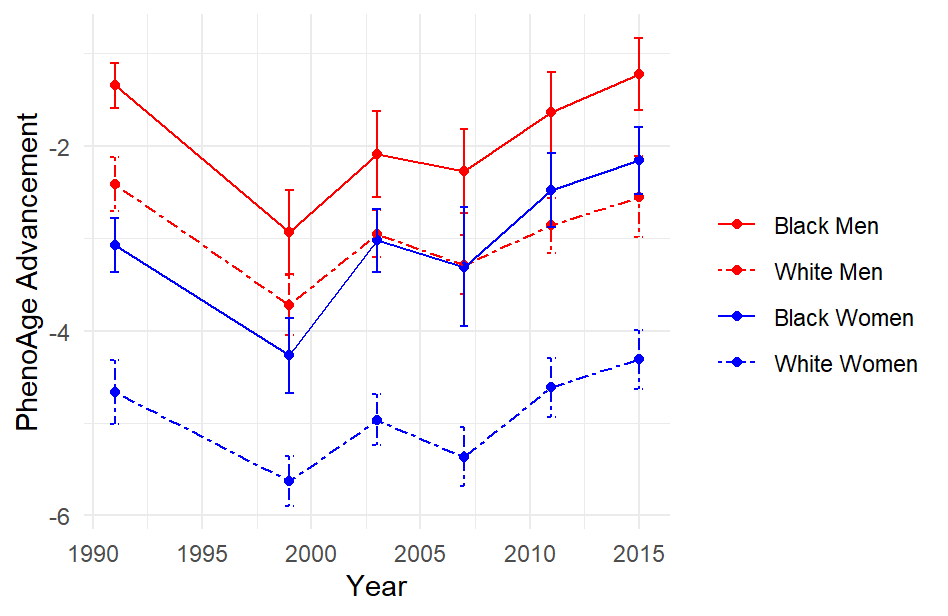
**Table 1. Characteristics of analytic sample, stratified by race and sex.** Our primary analytic sample included all participants in the 1999-2018 waves of continuous NHANES who provided blood samples during the Mobile Examination Center (MEC) exam and for whom biological aging measures could be calculated (n=29,487). Biological-aging algorithms were trained using NHANES III data and projected into the primary analytic sample.



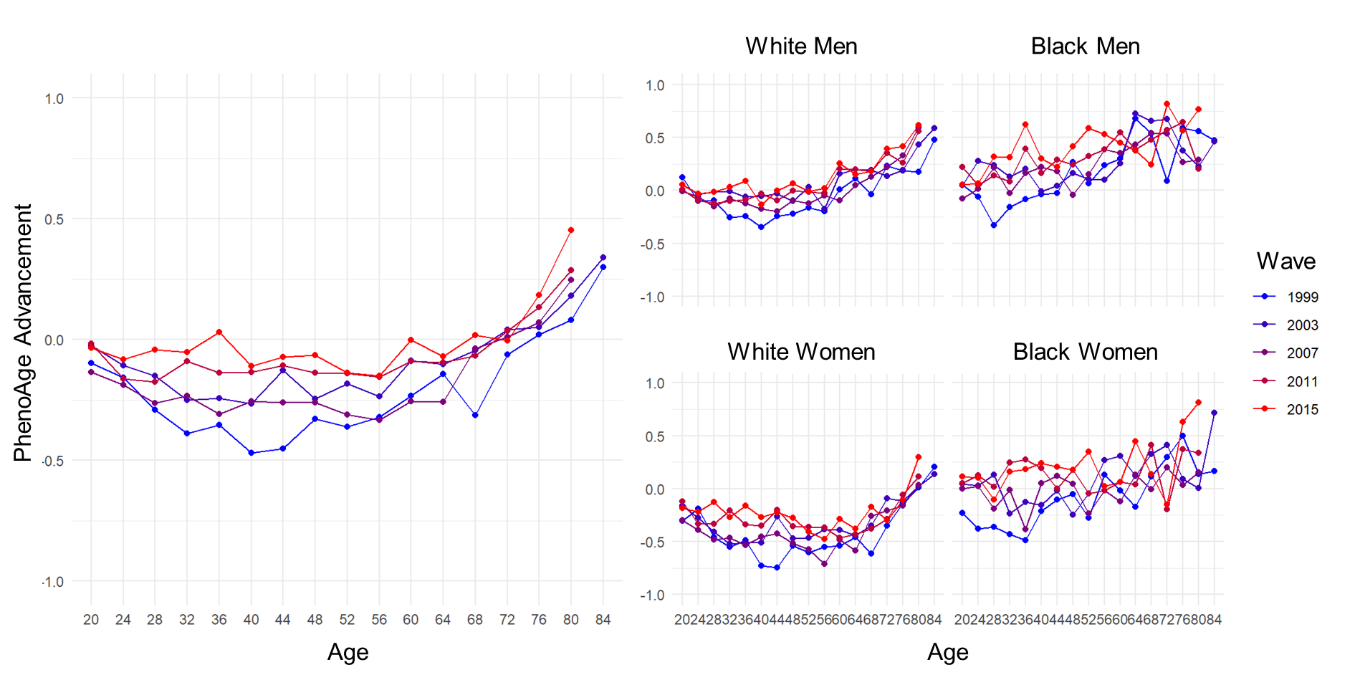
**Table 2.** **Results of APC decomposition using Bayesian Hierarchical Age-Period-Cohort models (PhenoAge).** APC decomposition was performed using three-factor Bayesian multilevel models, both in the full sample and separately by race-sex strata. We treated age as a level-1 fixed effect and period and cohort as level-2 random effects. Survey weights were log-transformed and included as a level-1 covariate while sampling strata and clusters were included as random effects. Effect-sizes are denominated in standard-deviation (SD) units of biological-age advancement, and are interpretable as the estimated independent effects of age, period, and cohort on biological aging. We tested the level of uncertainty around our estimates using 90% credible intervals (credible intervals excluding the null value are indicated using the \* symbol).



**Figure 1.** **PhenoAge advancement in among Black Americans and White Americans in the United States, NHANES III and continuous NHANES (1991-2018).** The figure shows mean biological-age advancements (measured using the PhenoAge algorithm), sample-weighted to the U.S. population at the time of measurement. Less-advanced biological aging values indicate that participants are physiologically younger, while more-advanced biological aging values indicate that participants are physiologically older. Population aging trajectories appeared to be improving over the 1990s, with the lowest values at the 1999-2002 measurement wave. Then, population aging trajectories appeared to reverse, reverting back to (or exceeding) early-1990s levels between 2012 and 2018.

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**Figure 2. Sample-weighted mean biological-age advancement by age and measurement wave (period) in analytic sample, 1999-2018.** The figure shows sample-weighted mean biological-age advancements at 4-year intervals of age and measurement wave. Potential cohort effects are revealed as non-linearities across waves of measurement. Here, more recent birth cohorts appear to have more advanced biological ages relative to earlier birth cohorts at the same chronological age (e.g., the average 35-year-old in 2015 had more advanced biological age than the average 35-year-old in 1999).



**Figure 3. Age, period, and cohort effects as estimated using three-factor Bayesian Hierarchical Age-Period-Cohort (BHAPC) models (PhenoAge).** The figure shows the independent effects of age, period, and cohort as estimated using fully specified Bayesian Hierarchical Age-Period-Cohort (BHAPC) models, both in the full sample and separately by race-sex strata. We treated age as a level-1 fixed effect and period and cohort as level-2 random effects; survey weights were log-transformed and included as a level-1 covariate while sampling strata and clusters were included as random effects. Effect-sizes are denominated in standard-deviation (SD) units of biological-age advancement, and are interpretable as the estimated effects of age, period, and cohort on biological aging.

