RESEARCH ARTICLE

Socioeconomic Status, Biological Aging, and Memory in a Diverse National Sample of Older US Men and Women

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Abstract

Background and Objectives

Exposure to socioeconomic disadvantage is associated with early-onset cognitive aging. Biological aging, the progressive loss of system integrity that occurs as we age, is proposed as a modifiable process mediating this health inequality. We examined whether socioeconomic disparities in cognitive aging in mid-to late-life adults is explained by accelerated biological aging similarly across race, ethnicity, and sex/gender.

Methods

Data were from a prospective cohort study of the US Health and Retirement Study DNA methylation substudy. Socioeconomic status (SES) was measured from years of education and household wealth at baseline. The extent and pace of biological aging were quantified using 3 DNA methylation measures: PhenoAge, GrimAge, and DunedinPoAm. Cognitive aging was measured from repeated longitudinal assessments of immediate and delayed word recall. Latent growth curve modeling estimated participants' level of memory performance and rate of decline over 2–11 follow-up assessments spanning 2–20 years. Multiple-group models were estimated to assess whether the relationship between SES and memory trajectories was mediated by biological aging across racial-ethnic by sex/gender subgroups.

Results

Data from a total of 3,997 adults aged 50–100 years were analyzed. Participants with lower SES had a lower memory performance, had a faster decline, and exhibited accelerated biological aging (SES effect size associations [β] ranged from 0.08 to 0.41). Accelerated biological aging was associated with decreased memory performance and faster memory decline (effect size range 0.03–0.23). SES-biological aging associations were the strongest for White men and women and weakest for Latinx women. The relationship between biological aging measures and memory was weaker for Black participants compared with that for White and Latinx people. In mediation analysis, biological aging accounted for 4%–27% of the SES-memory gradient in White participants. There was little evidence of mediation in Black or Latinx participants.

Discussion

Among a national sample of mid-to late-life adults, DNA methylation measures of biological aging were variably associated with memory trajectories and SES across White, Black, and Latinx mid-to late-life adults. These results challenge the assumption that DNA methylation biomarkers of aging that were developed in primarily White people can equivalently quantify aging processes affecting cognition in Black and Latinx mid-to late-life adults.

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Glossary

DNAm = DNA methylation; **HRS** = Health and Retirement Study; **PM** = proportion mediated; **SES** = socioeconomic status.

Aging and socioeconomic status (SES) are 2 important determinants of late-life cognitive health. Physicians often regard age and SES as immutable factors rather than quantities that could be modified to improve patient health. However, both may represent promising targets for intervention. Moreover, they may be connected.

The biological process of aging involves the progressive loss of system integrity, causing decreased resilience of cellular networks and organ systems, ultimately leading to disease and death.[1] The process of biological aging begins in early life[2] and manifests in variable rates of decline in organ-system integrity already in young adulthood.[3] In midlife adults, faster-paced decline in organ-system integrity is associated with signs of brain aging and cognitive decline.[4] Aging-related changes in brain integrity (e.g., cortical thinning and hippocampal atrophy) are accompanied by decline in cognitive performance.[5]

Low SES, commonly measured from wealth, income, occupational status, and/or educational experience, is associated with an earlier onset and faster pace of aging-related changes in the brain.[6,7] The mechanism by which SES inequalities affect health may be through acceleration of the aging process through repeated adaptation to stressors that cause cumulative wear and tear on the body's system and increase vulnerability to multiple disease processes.[8,9] Until recently, we have not had a way of comprehensively measuring these processes. DNA methylation (DNAm) biomarkers that quantify molecular alterations that occur with aging provide promising tools for measuring SES inequalities in aging. Several proposed measures indicate more advanced biological aging in individuals with greater socioeconomic disadvantage.[10-13] Some of these measures have also been associated with cognitive performance in small samples.[10,13,14] However, it is unclear whether DNAm patterns mediate the relationship between SES and late-life cognitive health.

There is no gold standard measure of biological aging; several methods have been proposed based on different biological measurements and analytic strategies.[15] Three recently developed measures of biological aging have gained popularity in the literature and have been consistently associated with SES and cognitive aging: 2 DNAm clocks, PhenoAge[16] and GrimAge,[17] and the DunedinPoAm[10] pace of aging measure. DNAm clocks measure methylation levels at different age-related CpG sites to quantify an individual's biological age. PhenoAge was developed using the Infinium Methylation EPIC array to capture clinical measures to increase the accuracy of morbidity predictions.[16] GrimAge uses plasma protein predictors to identify 1,030 CpG sites that forecast time-to-death due to all-cause mortality.[17] A more recent aging index, DunedinPoAm, uses DNAm signatures to capture within-individual variation in the pace of aging of health-relevant systems. Unlike the other 2 methylation clocks, this index records how much time has passed; it is designed to function as a speedometer, recording how fast the individual is aging.[10]

Most research on DNAm biomarkers of aging has focused non-Latinx White samples and for whom the spectrum of socioeconomic variation may be limited relative to what exists in the United States. Furthermore, population subgroup differences in the pathways that link SES to cognition may be present at the intersection of race, ethnicity, and sex/gender groups, which is critical to consider for potential intervention on SES or biological aging. To address these gaps in the literature, this study was conducted to examine associations between SES, 3 DNAm biomarkers, and memory trajectories in a representative national sample of mid-to late-life adults. We hypothesize that these measures of biological aging will mediate the relationship between SES and late-life memory trajectories similarly across racial-ethnic-sex/gender subgroups.

Methods

Participants

The Health and Retirement Study (HRS) is a nationally representative longitudinal study of Americans older than 50 years, designed to examine the health, social, and economic factors associated with aging.[18] Data collection began in 1992, with the initial cohort born between 1931 and 1941 (aged 51–61 years in 1992). In 1993, a second cohort was added consisting of individuals born before 1924 (aged 70 years or older in 1993). Two additional cohorts were added in 1998 to address age gaps and create a representative sample of those older than 50 years. These additional cohorts consist of individuals born between 1924 and 1930 and 1942–1947, respectively. Since then, a new cohort of individuals aged 51–56 years has been continually added to the HRS sample every 6 years (2004, 2010, and 2016). The HRS oversamples Black and Hispanic/Latino/a/x/e (Latinx, hereafter) participants to improve the reliability of estimates. Additional details of the HRS sample may be found elsewhere.[19]

Participants are followed up every 2 years to complete core interviews. These core interviews consist of content including (but not limited to) the following: demographics, assets and income, physical conditions and treatment, health behaviors, cognitive function, among others.[18] In 2016, alive HRS participants were asked to consent to a venous blood draw, of which samples from 9,934 participants were collected (65% completion rate among eligible cases).[20] DNAm assays were performed on a subsample of these participants (n = 4,104);

approximately 98% passed quality control checks (n = 4,018). This DNAm sample is representative of the entire HRS sample. Participants were excluded from the current analyses if they were missing data on race and ethnicity (n = 2) and years of education (n = 19). The remaining sample (n = 3,997) included 1,165 non-Latinx White men, 1,504 non-Latinx White women, 224 non-Latinx Black men, 433 non-Latinx Black women, 223 Latinx men, 328 Latinx women, and 47 men and 73 women who identified their ethnicity as non-Latinx and race as other.

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from all participants in the HRS study. Ethical approval for the HRS was obtained from the University of Michigan institutional review board.

Measures

Measures of Biological Aging

The 3 aging measures are described in detail in the eMethods, links.lww.com/WNL/C296.

In short, the PhenoAge and GrimAge clocks estimate the age at which a person's mortality risk would be approximately normal in their respective reference samples: PhenoAge was developed in the US National Health and Nutrition Examination Survey III and Invecchiare in Chianti studies,[16] GrimAge was developed in the Framingham Heart Study Offspring cohort.[17] Both clocks were developed using 2-step approaches that involved modeling physiologic parameters (clinical chemistries and complete blood count data for PhenoAge, blood proteins for GrimAge) and mortality risk. Clock ages that are older than the chronological age of the person being measured indicate an advanced state of biological aging; younger clock ages indicate delayed aging.[21] For analysis, HRS participants' DNAm clock ages were regressed on their chronological ages, and residual values were computed. These residual values, referred to as "age acceleration residuals," were standardized to mean = 0, SD = 1. Age acceleration residual values greater than 0 indicate higher than expected biological aging based on chronological age; values less than 0 indicate lower than expected biological age.

DunedinPoAm estimates a person's pace of aging, the rate of decline in system integrity that occurs with advancing chronological age. DunedinPoAm was developed by analyzing longitudinal change in 18 biomarkers tracking multiorgan-system integrity in a birth cohort followed up from ages 26–38 years.[10] Values are interpretable as years of physiologic change occurring per 12-month calendar interval in healthy adults. DunedinPoAm values > 1 indicate a faster than normal pace of aging; values <1 indicate a slower pace of aging. For analysis, values of DunedinPoAm were standardized to mean = 0, SD = 1.

Race, Ethnicity, and Sex/Gender

HRS collected information about self-reported primary race and ethnicity by (1) asking participants whether they were Hispanic or Latino; and (2) asking participants to classify themselves racially as White, Black, Asian, American Indian, Alaska Native, or Pacific Islander. Participants were only asked to self-report whether they were male or female. We use the term sex/gender because it is unknown whether individuals actually reported their biological sex or their gender identity.[22]

Socioeconomic Status

An SES composite was created based on measures collected during the first study visit. Years of education was measured by the highest self-reported completed grade of school. We calculated birth cohort–based education standardized scores (z scores) by subtracting each participant's years of education by the mean education for their birth cohort and dividing by its SD. Wealth was measured by *total wealth* available in the RAND corporation HRS dataset income and wealth imputation dataset.[23] *Total wealth* was adjusted for inflation using the consumer price index[24] to calculate inflation relative to 2012 and converted all other waves to 2012 dollars.[25] We then transformed these scores using the inverse hyperbolic sine.[26] Z scores were created for wealth based on 5-year age groups (i.e., 50–54, 55–59, 60–64, etc.) for each study wave to adjust for age and period effects. Education and wealth z scores were averaged to represent the SES composite.

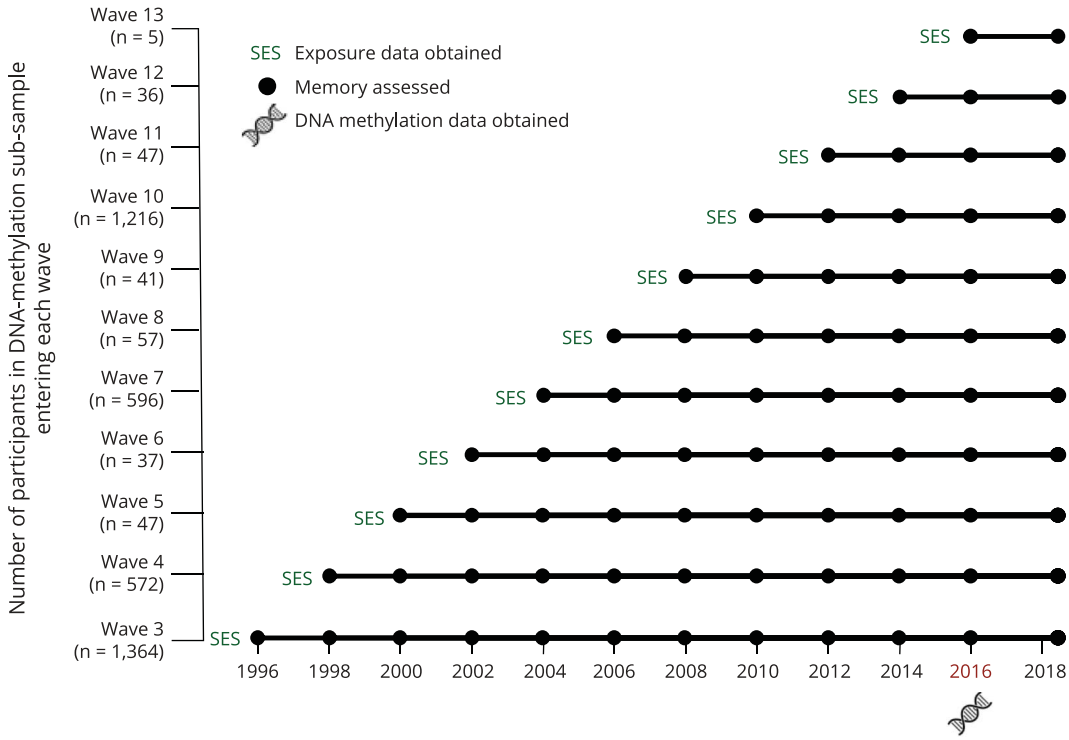
Memory Performance

Memory was assessed through the immediate and delayed recall scores of the Consortium to Establish a Registry for Alzheimer's Disease[27] 10-item word list memory test. Only data from Wave 3 (1996) or later were used because this was the first wave the 10-item memory test was administered. HRS RAND data include imputed cognitive scores for respondents who participated in a given wave but were missing cognitive data. We restricted longitudinal data to visits that respondents were aged older than 50 years. Raw scores on immediate and delayed recall trials were converted into z scores using the mean values and SDs at Wave 13 (2016). Composite scores were computed by averaging these z scores at each occasion because this method has been shown to improve reliability[28] and contains much of the same information as a common memory factor score.[29]

Statistical Analyses

Figure 1 depicts the timing of measurements included in analyses described further. Data from 1996 to 2018 were used to model memory trajectories through a latent growth curve model that included age and study wave at first memory assessment as covariates. To derive estimates of memory functioning when DNA samples were collected, performance at the 2016 visit was used as the growth curve model intercept. Time was also centered at the 2016 visit, indicating the amount of time each visit occurred in years from 2016. Thus, intercepts indicate memory performance when DNA samples were collected, and slopes indicate the average rate of decline throughout the study. Models allowing only linear change fit better than those allowing both linear and quadratic slopes. Intercept and slope estimates were saved for each participant

Figure 1 Timing of Measurements Included in the Study



and used as outcomes in subsequent models to avoid multicollinearity issues.[30]

We estimated a series of models to evaluate independent relationships between each DNAm indicator, SES, and memory intercept and slope. Next, mediation analyses were conducted, separately for each DNAm indicator. For these models, we specified paths between (1) SES and the DNAm indicator, (2) the DNAm indicator and memory outcomes, and (3) SES to the memory outcomes. The indirect effect was calculated as the product of the coefficients corresponding to the path between SES and DNAm indicator and the path between DNAm indicator and memory.[31] Mediation effects were examined using the products of coefficient approach with bootstrapping.[32] Standardized parameter estimates and proportion mediated (PM; proportion of the effect of SES on memory trajectories mediated through the biological aging measure) were reported. Sampling weights for the 2016 Venous Blood Study were used to obtain population-based estimates.

Each model was first estimated across the entire sample. To examine racial-ethnic-sex/gender subgroup differences, we used known-class mixture models with racial-ethnic-sex/gender subgroups as known classes. This known grouping variable is incorporated as a moderator variable, allowing model parameters to vary as a function of membership in the identified groups.[33] Subgroup differences were examined using the "Model Constraint" option in Mplus. Multiple-group models were estimated only for White, Black, and Latinx men and women (N = 3,877) because sample sizes of the other racial-ethnic-sex/gender subgroups were too small for this type of analysis.

Additional analyses were conducted to examine relationships between individual components of the SES composite with memory and the biological aging indicators. Given that the memory decline outcome in our analyses contains information from measurements before measurement of the biological aging indicators, sensitivity analyses were conducted, restricting the sample to the subset with available 2018 data. Latent difference score analyses were used to model change in memory performance between the 2016 and 2018 visits. The derived change score was regressed on SES, and the biological aging indicators and mediation models were conducted according to the procedures described earlier.

All analyses were performed using Mplus version 8.5.[34] Both p values and CIs were used to determine statistical significance.[35] Bootstrapping (1,000 bootstrapped samples) was used to obtain 95% CIs of all direct and indirect effects. A p value of 0.01 (i.e., 99% CI) was used for multiple group comparisons to decrease the likelihood of type I error.

Data Availability

The datasets used for analyses are available from the HRS website (hrs.isr.umich.edu/dataproducts/access-to-public-data).

Results

Characteristics of the full sample and the 6 racial-ethnic-sex/gender subgroups are summarized in Table 1. Participants had an average of 4.2 (SD = 3.1) visits with cognitive data. Black men demonstrated the lowest 2016 memory performance and

Table 1 Sample Characteristics

Characteristics	Entire sample (N = 3,997)	White men (N = 1,165)	White women (N = 1,504)	Black men (N = 224)	Black women (N = 433)	Latinx men (N = 223)	Latinx women (N = 328)
Age, mean (SD)	69.89 (9.6)	71.45 (9.5)	70.98 (9.8)	67.07 (8.4)	66.31 (8.7)	66.13 (8.0)	65.75 (9.0)
Study y, mean (SD)[a]	13.18 (6.3)	13.98 (6.1)	14.73 (5.9)	10.22 (5.9)	10.75 (6.2)	9.85 (5.9)	10.76 (6.4)
Years of education, mean (SD)	13.30 (2.6)	13.71 (2.5)	13.44 (2.3)	12.50 (2.7)	12.72 (2.6)	9.88 (4.6)	9.11 (4.7)
Wealth, mean (SD)[b]	−0.03 (1.0)	0.22 (0.9)	0.22 (0.9)	−0.64 (0.8)	−0.58 (0.9)	−0.55 (0.9)	−0.53 (1.0)
SES, mean (SD)	−0.02 (0.8)	0.25 (0.7)	0.20 (0.7)	−0.38 (0.7)	−0.30 (0.6)	−0.76 (0.9)	−0.85 (1.0)
Epigenetic clocks							
PhenoAge residual, mean (SD)	−0.01 (0.9)	0.07 (0.9)	−0.10 (1.0)	0.01 (1.0)	0.27 (1.1)	0.11 (0.9)	−0.02 (0.9)
GrimAge residual, mean (SD)	−0.003 (1.0)	0.34 (1.0)	−0.36 (0.9)	0.67 (1.1)	0.06 (0.9)	0.33 (0.9)	−0.32 (0.8)
DunedinPoAm	1.08 (0.1)	1.07 (0.1)	1.06 (0.1)	1.11 (0.1)	1.09 (0.1)	1.09 (0.1)	1.06 (0.1)
Memory performance, mean (SD)	−0.03 (0.6)	−0.12 (0.6)	0.19 (0.6)	−0.41 (0.6)	−0.11 (0.6)	−0.31 (0.6)	−0.10 (0.6)
Memory decline, mean (SD)	−0.24 (0.2)	−0.27 (0.2)	−0.25 (0.2)	−0.23 (0.2)	−0.21 (0.2)	−0.21 (0.2)	−0.18 (0.2)

Abbreviation: SES, socioeconomic status composite variable (*z* score).
[a] Years in study with cognitive data.
[b] Values reported are the *z* scores for the total wealth variable.

White women had the highest. White men and women were older in 2016, completed more study visits, and demonstrated steeper rates of memory decline compared with Black and Latinx participants (p values < 0.001).

SES and Memory Trajectories

Overall, a 1 SD increase in SES increases 2016 memory performance by 0.41 (0.37–0.44) SDs and lowers the rate of memory decline by 0.16 (0.12–0.20) SDs. Higher SES was associated with higher memory level and a slower rate of decline across race-ethnicity-sex/gender (Figure 2). The relationship between SES and 2016 memory was stronger for Black women compared with that for White women (β_{diff} = −0.11 [−0.18 to −0.02]). For Latinx women, SES had a stronger relationship with memory decline when compared with that for White men (β_{diff} = −0.04 [−0.07 to −0.02]).

SES and Biological Aging

Participants' DNAm clock ages were correlated with their chronological ages (PhenoAge r = 0.73; GrimAge r = 0.83). DunedinPoAm was not correlated with chronological age (r = 0.02). PhenoAge indicated that Latinx and White men had the most-advanced aging and Latinx and White women had the most delayed aging (Table 1). GrimAge and DunedinPoAm indicated that Black men had the fastest biological aging and White and Latinx women had the slowest aging (p-values < 0.001).

An SES gradient in biological aging was noted in the entire sample, where higher SES was associated with slower aging for each DNAm measure (PhenoAge β = −0.08 [−0.12 to −0.04]; GrimAge β = −0.27 [−0.31 to −0.23]; DunedinPoAm β = −0.21 [−0.25 to −0.17]). The SES-PhenoAge gradient was present among White women (Figure 3) and was stronger than the gradient among Latinx men (β_{diff} = −1.09 [−2.39 to −0.33]) and Latinx women (β_{diff} = −0.83 [−2.01 to −0.28]). For GrimAge, the SES-biological aging gradient was present for all groups except Latinx women, and estimates were stronger for White men (β_{diff} = −1.61 [−2.48 to −0.95]), White women (β_{diff} = −1.30 [−1.97 to −0.67]), and Black women (β_{diff} = −1.02 [−2.0 to −0.16]) compared with those for Latinx women. A similar pattern of group differences was noted for DunedinPoAm, where the relationship with SES was stronger for White men (β_{diff} = −0.20 [−0.04 to −0.01]), White women (β_{diff} = −0.02 [−0.03 to −0.01]), and Black women (β_{diff} = −0.02 [−0.04 to −0.01]) compared with that for Latinx women. An examination of education and wealth as separate predictors of the biological aging measures revealed weaker associations than using the composite measure, with a few exceptions: relationships between wealth and GrimAge were stronger for Latinx men (β = −0.18 [−0.33 to −0.02]) and women (β = −0.11 [−0.24 to 0.02]) and between wealth and PhenoAge for Black men (β = −0.08 [−0.25 to 0.11]) compared with estimates for the overall SES composite.

Biological Aging and Memory Trajectories

Overall, accelerated biological aging was associated with a lower 2016 memory performance (PhenoAge β = −0.08 [−0.12 to −0.04]; GrimAge β = −0.23 [−0.27 to −0.20]; DunedinPoAm β = −0.15 [−0.19 to −0.11]). More-advanced PhenoAge (β = −0.04 [−0.09 to −0.001]) and GrimAge (β = −0.10 [−0.13 to −0.06]) and faster DunedinPoAm (β = −0.07 [−0.12 to −0.03]) were associated with faster memory decline. Associations of DNAm measures of aging with 2016 memory performance (Figure 4) and memory decline (Figure 5) varied across race/ethnic-sex/gender groups. PhenoAge was only reliably associated with 2016 memory performance for White women. Older

Figure 2 Socioeconomic Gradients in Memory Level and Decline Across Racial-Ethnic-Sex/Gender Subgroups

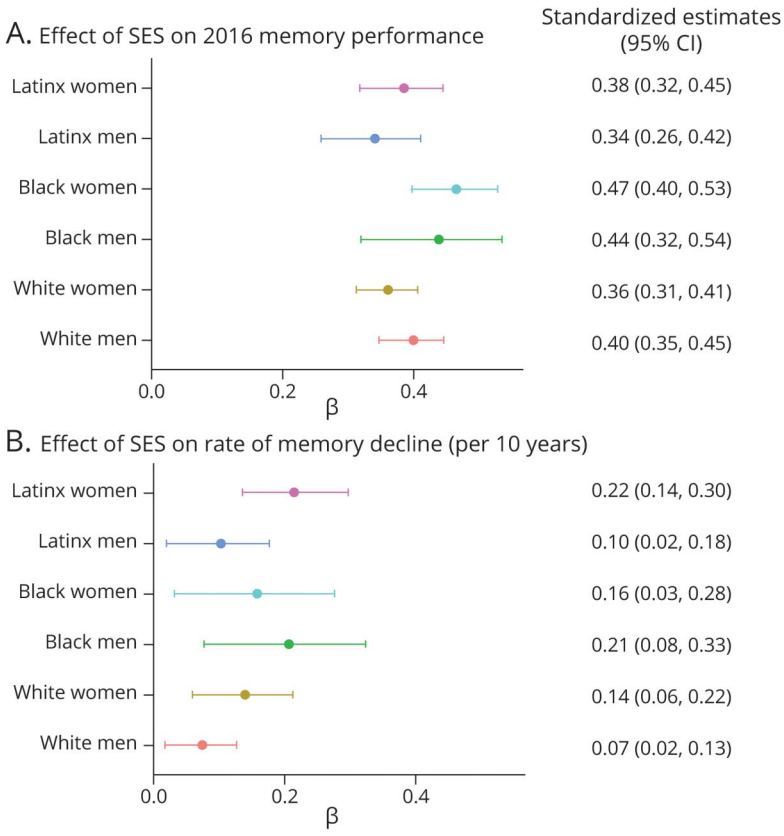
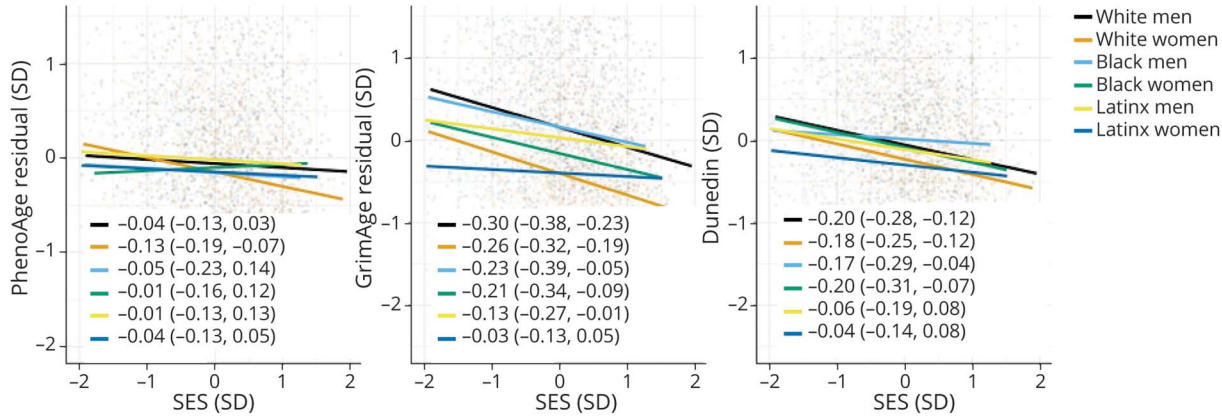


Figure 2 plots effect sizes for associations between SES and memory trajectories estimated across race/ethnicity-sex/gender subgroups. The x-axis represents the effect size estimate. The figure shows that each SD increase in SES was associated with 0.34–0.47 SD higher scores on 2016 memory performance (top panel) and 0.07–0.22 SD less decline in memory scores per 10-year follow-up period in the study. SES = socioeconomic status.

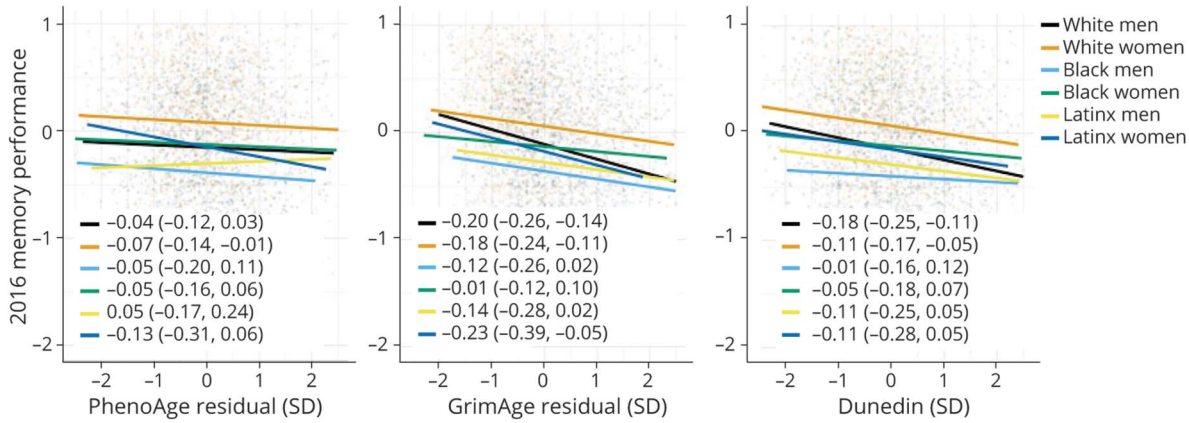
GrimAge and Higher DunedinPoAm values were associated with a lower 2016 memory performance and faster memory decline for White men and women. While many of the relationships between biological aging indicators and memory performance were the strongest for Latinx women, estimated CIs were wide, suggesting lack of precision of the estimated effects. Black women consistently demonstrated the weakest associations between DNAm measures and memory trajectories. Reliable group differences were noted for the relationship between GrimAge and memory trajectories between Black women and White men (2016 Memory $\beta_{diff} = -0.030$ [−0.05 to −0.01]; Memory Decline $\beta_{diff} = -0.006$ [−0.011 to −0.001]),

Figure 3 Socioeconomic Gradients in DNA Methylation Measures of Aging Across Racial-Ethnic-Sex/Gender Subgroups



Scatterplots showing associations between SES (x-axis) and each DNAm measure (y-axis) across racial-ethnic-sex/gender subgroups. Higher values on PhenoAge, GrimAge, and Dunedin indicate accelerated biological aging. SES = socioeconomic status.

Figure 4 Relationship Between DNA Methylation Measures of Aging and Memory Level Across Racial-Ethnic-Sex/Gender Subgroups



Scatterplots showing associations between each DNAm measure (x-axis) and 2016 memory performance (y-axis) across racial-ethnic-sex/gender subgroups.

White women (2016 Memory β_{diff} = −0.022 [−0.039 to −0.005]; Memory Decline β_{diff} = −0.008 [−0.014 to −0.002]), and Latinx women (2016 Memory β_{diff} = −0.030 [−0.052 to −0.007]; Memory Decline β_{diff} = −0.009 [−0.017 to −0.002]) and for DunedinPoAm and 2016 memory between White men and Black men (β_{diff} = −1.17 [−2.32 to −0.118]) and women (β_{diff} = −0.918 [−1.61 to −0.235]).

Mediation Analyses

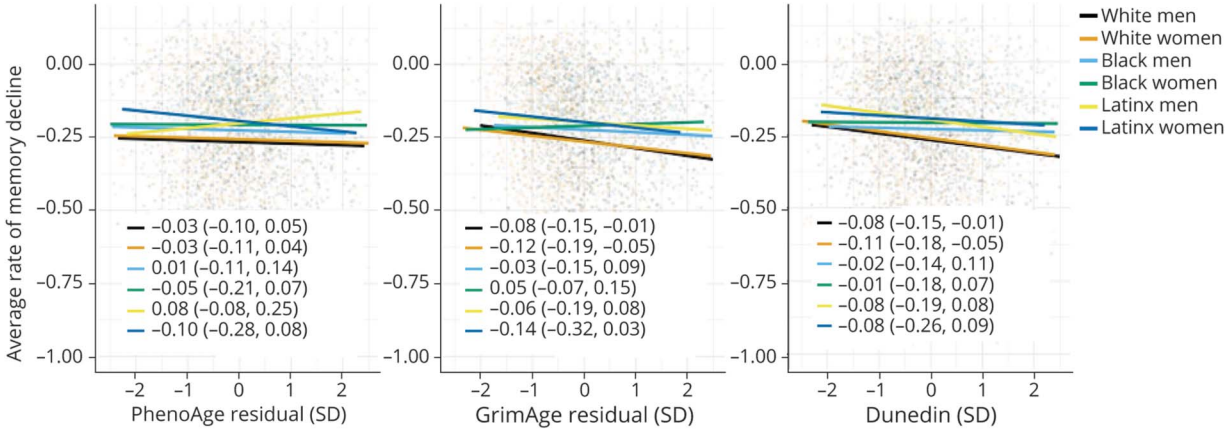
Mediation models were estimated for each DNAm measure separately. Each DNAm measure partially mediated the SES gradient on 2016 memory performance (PhenoAge indirect effect = 0.003 [0.001–0.006]; GrimAge indirect effect = 0.031 [0.025–0.039]; DunedinPoAm indirect effect = 0.014 [0.009–0.019]). PM estimates indicated that GrimAge (PM = 11%) conveyed a larger portion of the SES gradient than DunedinPoAm (PM = 5%) or PhenoAge (PM = 1%). GrimAge (indirect effect = 0.013 [0.006–0.020]; PM = 24%) and DunedinPoAm (indirect effect = 0.010 [0.005–0.016]; PM = 18%) partially mediated the SES-memory decline gradient.

Standardized indirect effect estimates for the PhenoAge models were small across race-ethnicity-sex/gender groups (Figure 6). Compared with the other groups, GrimAge and DunedinPoAm mediated larger proportions of the SES gradient in memory level and decline for White men and women.

Sensitivity Analyses

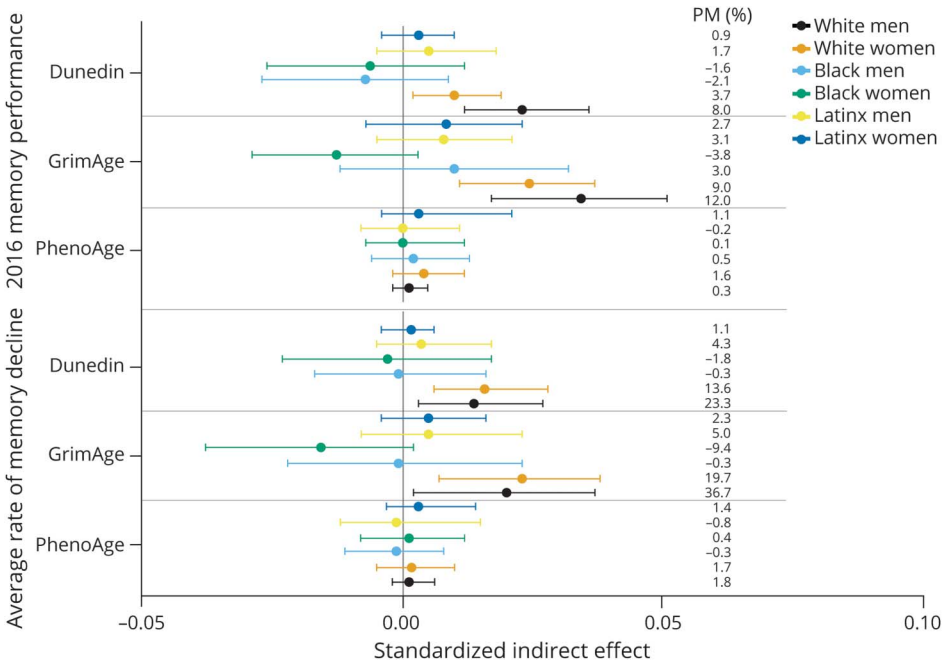
Sensitivity analyses examining change in memory performance from 2016 to 2018 revealed a similar pattern of associations compared with the main analyses. Specifically, higher SES (β = 0.16 [0.12–0.19]), less-advanced PhenoAge (β = −0.03 [−0.06 to 0.004]) and GrimAge (β = −0.08 [−0.11 to −0.05]), and slower DunedinPoAm (β = −0.05 [−0.09 to

Figure 5 Relationship Between DNA Methylation Measures of Aging and Memory Decline Across Racial-Ethnic-Sex/Gender Subgroups



Scatterplots showing associations between each DNAm measure (x-axis) and memory decline (y-axis) across racial-ethnic-sex/gender subgroups.

Figure 6 Indirect Effect Estimates From Mediation Analyses Across Racial-Ethnic-Sex/Gender Subgroups



−0.02]) were associated with a smaller decrease in change from 2016 to 2018. Indirect effect estimates were similar to those reported for the SES-memory decline gradient (PhenoAge: β = 0.001 [−0.001 to −0.004]; GrimAge: β = 0.014 [0.01–0.02]; DunedinPoAm β = 0.006 [0.001–0.013]).

Discussion

DNAm biomarkers of aging are emerging as a powerful approach for understanding how social exposures, such as SES, are embodied to shape health in aging. We tested how 3 DNAm measures representing the extent and pace of biological aging related to the socioeconomic gradient in memory trajectories in a nationally representative sample of mid-to late-life adults. There were 4 main findings: (1) socioeconomic gradients in biological aging were present–those with more wealth and more years of school exhibited less-advanced biological aging; (2) accelerated biological aging was associated with a lower 2016 memory performance and faster memory decline; (3) biological aging mediated a portion of the socioeconomic gradient in memory level and decline; and (4) magnitudes of associations between SES, biological aging, and memory trajectories varied across race-ethnicity-sex/gender.

Our finding that higher SES was associated with less-advanced/slower biological aging among people in the United States extends observations from studies of White and European samples.[10-13] They also highlight potential heterogeneity in these associations in populations with different social lifecourse exposures. We found that, consistent with previous studies in non-White US populations,[36] GrimAge and DunedinPoAm demonstrated the expected SES gradient among some of the non-White groups in our study. Only White women showed the expected SES gradient in PhenoAge. Our findings were less consistent among Latinx women and men, although sample sizes for these analyses were small.

DNAm clocks and related measures, such as the DunedinPoAm pace of aging, represent a cutting-edge approach to quantifying biological aging in epidemiologic and clinical studies.[37] So far, few studies have described how these measurements relate to the process of cognitive aging. In the large US representative sample we analyzed, mid-to late-life adults with more advanced biological aging demonstrated a lower memory performance and faster memory decline than those of the same chronological age with less advanced/slower biological aging. This finding expands on observations from smaller, primarily White European and New Zealand samples,[10,13,14] which established a link between the extent and pace of biological aging and later-life memory decline.

Effect sizes were small for associations of DNAm measures of aging with cognitive trajectories and varied between the different measures of aging and across racial-ethnic-sex/gender strata. Both biological aging and memory are measured imprecisely. It is notable that, among the 3 measures we tested, effect sizes were consistently the largest for the GrimAge clock, which shows substantially higher measurement reliability when compared with those for the PhenoAge Clock and DunedinPoAm.[38,39] New methods to develop more reliable DNAm measures of aging[38,39] may reveal stronger relationships. Nevertheless, our findings encourage a cautious approach to integrating these novel measures of biological aging into research on cognitive aging, especially in Black Americans.

Comparisons of associations across race/ethnic-sex/gender groups revealed stronger relationships between the biological aging measures and memory trajectories among White men and women when compared with Black men and women and among Latinx women compared with Black women. Racially patterned lifecourse social experiences that influence cognitive trajectories may shape epigenetic processes differently across racial and ethnic groups, and such profiles may not be adequately represented with these current DNAm measures. Racism is associated with exposure to a myriad of acute and chronic stressors that accumulate over the lifecourse and accelerates physiologic deterioration.[40] These stress pathways have been linked to age-related memory decline among Black Americans, independent of SES.[41] More research is needed to determine whether the cumulative stress exposure experienced by Black people is associated with distinct epigenetic pathways (e.g., associated with different CpG sites or differentially methylation regions).

Even among White men and women, the DNAm measures mediated only a small fraction of the SES gradient in aging-related memory decline. This small mediation fraction could reflect limitations of the simple mediation models tested in this study.[42] For example, it is possible that the primary effect of biological aging is on other intermediary factors (e.g., cardiovascular disease) on the pathway linking SES to memory trajectories. In addition, molecular pathways[43] not captured in DNAm measures of aging may be more salient biological links between SES and late-life memory.

Previous work has documented sex/gender differences in biological aging processes,[21,44] with women having lower epigenetically predicted biological ages compared with men. However, findings for sex/gender differences in associations of SES with biological aging are inconsistent.[12,45] In our study, we used an intersectional approach[46] comparing racial-ethnic-sex/gender subgroups that revealed a more complex pattern of differences, highlighting contrasts between groups at the extremes of social power. White men showed stronger SES-biological aging associations compared with Latinx women and stronger biological aging-memory trajectory associations compared with Black women. While White and Latinx women demonstrated delayed/slower aging compared with men, Black women tended to show biological aging that was similar to that of men. Taking an intersectional approach may provide a more nuanced understanding of the links between SES, biological aging, and cognitive health outcomes.

This study provides preliminary evidence on the utility of 3 DNAm measures in quantifying biological aging pathways that link SES to cognition among Black and Latinx women and men. We cannot be sure that our findings generalize because of the relatively small number of Black and Latinx HRS participants with DNAm measures. Larger samples are needed to generate more precise estimates (i.e., smaller CIs).[47]

SES does not capture all upstream structural disadvantages faced by minoritized populations. Societies foster racial discrimination through systems that affect housing, education, employment, earnings, and health care.[48] Future studies should include measures of upstream structural determinants, such as structural racism[48] and sexism,[49] to better understand how social disadvantages influence biological aging processes among minoritized communities.

Another study limitation is that each DNAm measure was obtained at a single point in time. While steeper decline in memory throughout the study was associated with more advanced biological aging in 2016, analyses cannot rule out reverse causation (i.e., poor memory performance contributing to advanced biological aging). Results from sensitivity analyses with change from 2016 to 2018 as the outcome were similar to those demonstrated for the rate of memory decline, providing some evidence against reverse causation. Among those who consented to the 2016 Venous Blood Study, Latinx and Non-Latinx Black participants were less likely than Non-Latinx White Participants to complete the study.[20] While the sampling weights used in the current analyses account for differential participation by age, sex/gender, race, and ethnicity, it is unclear whether SES drove differential study participation.

Among a nationally representative sample of mid-to late-life adults in the United States, more advanced/faster biological aging, as measured by the GrimAge DNAm clock and DunedinPoAm pace of aging, was associated with lower scores on memory tests and faster decline in memory functioning over time. GrimAge and DunedinPoAm also indicated more advanced and faster aging in mid-to late-life adults with lower SES. Biological aging measures mediated only small fractions of the SES gradient in aging-related memory decline. Moreover, associations of biological aging measures with memory trajectories were consistent only in Whites but not in Black or Latinx people. DNAm biomarkers of aging have the potential to provide surrogate endpoints for interventions that aim to prevent aging-related functional decline, including cognitive decline, but lose that potential if their utility is limited to White people.[50]

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