Title

Discordant Biological and Chronological Age: Implications for Cognitive Decline and Frailty.

Journal

The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 78(11)

Authors

Shaaban, C
Rosano, Caterina
Zhu, Xiaonan
et al.

Publication Date

2023-10-28

DOI

10.1093/gerona/glad174

Peer reviewed

The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences, 2023, **78**(11), 2152–2161
https://doi.org/10.1093/gerona/glad174
Advance access publication 22 July 2023
Research Article

Discordant Biological and Chronological Age: Implications for Cognitive Decline and Frailty

C. Elizabeth Shaaban, PhD,[1,*] Caterina Rosano, MD,[1] Xiaonan Zhu, PhD,[1] Bret R. Rutherford, MD,[2] Kailyn R. Witonsky, BA,[1] Andrea L. Rosso, PhD,[1] Kristine Yaffe, MD,[3,4] and Patrick J. Brown, PhD[2]

[1]Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.
[2]Neurobiology and Therapeutics of Aging Division, Columbia University College of Physicians and Surgeons, New York State Psychiatric Institute, New York, New York, USA.
[3]Department of Epidemiology and Biostatistics, University of California, San Francisco, California, USA.
[4]Departments of Psychiatry and Neurology, University of California, San Francisco, California, USA.

*Address correspondence to: C. Elizabeth Shaaban, PhD. E-mail: Beth.Shaaban@pitt.edu

Decision Editor: Lewis A. Lipsitz, MD, FGSA (Medical Sciences Section)

Abstract

Background: Older adults with discordant biological and chronological ages (BA and CA) may vary in cognitive and physical function from those with concordant BA and CA.

Methods: To make our approach clinically accessible, we created easy-to-interpret participant groups in the Health, Aging, and Body Composition Study ($N = 2\,458$, 52% female participants, 65% White participants, age: 73.5 ± 2.8) based on medians of CA, and a previously validated BA index comprised of readily available clinical tests. Joint models estimated associations of BA–CA group with cognition (Modified Mini-Mental State Examination [3MS] and Digit Symbol Substitution Test [DSST]) and frailty over 10 years.

Results: The sample included the following: 32%, Young group (BA and CA < median); 21%, Prematurely Aging group (BA ≥ median, CA < median), 27%, Old group (BA and CA ≥ median), and 20%, Resilient group (BA < median, CA ≥ median). In education-adjusted models of cognition, among those with CA < median, the Prematurely Aging group performed worse than the Young at baseline (3MS and DSST $p < .0001$), but among those with CA ≥ median, the Resilient group did not outperform the Old group (3MS $p = .31$; DSST $p = .25$). For frailty, the Prematurely Aging group performed worse than the Young group at baseline ($p = .0001$), and the Resilient group outperformed the Old group ($p = .003$). For all outcomes, groups did not differ on change over time based on the same pairwise comparisons ($p \geq .40$).

Conclusions: Discordant BA and CA identify groups who have greater cognitive and physical functional decline or are more protected than their CA would suggest. This information can be used for risk stratification.

Keywords: Biological aging, Executive function, Global cognition, Physical function

Various methods of quantifying biological aging have been developed by aggregating indicators of the integrity of bodily systems (1–9). Biological aging can be measured in teens all the way through centenarians (7,8,10), and has been evaluated across a range of locations and ethnicities including Canada, China, New Zealand, Singapore, Sweden, Taiwan, and the United States (4–8,11–18). Greater biological aging has been associated with greater mortality and poorer physical and cognitive function (4,5,8,11–17,19,20).

Using a modified version of the Klemara–Doubal measure of biological age (BA) (9), we have recently shown that BA, but not chronological age (CA), is associated both with greater severity of depressive symptoms and greater risk of increasing depressive symptoms over time in older adults (21). Others have shown that BA algorithms predict mortality and incident frailty better than CA (8,18,22,23). BA is clearly important for health outcomes, but it does not exist in isolation. Rather it operates on a background of the nonmodifiable CA. Different combinations of BA and CA may influence changes in cognitive and physical function over time. Understanding how can inform risk stratification and future research into resilient aging. This is critical in supporting older adults' independence. Therefore, we tested both cognitive and physical trajectories over time based on combined BAs and CAs of older adults, with a particular interest in groups whose BA and CA were discordant (ie, the "Prematurely Aging" group (BA ≥ median, CA < median), and the "Resilient" group (BA < median, CA ≥ median). By comparing groups with the same CA but different BAs, we can identify the importance of BA at both younger and older CAs. We hypothesized that a Prematurely Aging group would demonstrate greater cognitive impairment and frailty burden at baseline and greater worsening over time compared with those who were <median on both BA and CA ("Young" group). Furthermore, we hypothesized that the Resilient group would have better cognitive performance and less frailty burden at baseline and

Received: November 22 2022; Editorial Decision Date: July 13 2023.

demonstrate less deterioration on these indices compared with those who were ≥ median on both BA and CA ("Old" group). A key aim was to make this work accessible to clinicians, so we employed clinically available tests to construct our marker of BA and easy-to-interpret variable coding and modeling approaches.

Method

Participants

This is a secondary analysis of existing data from the Health, Aging, and Body Composition (Health ABC) Study (24). Community-dwelling older adults were recruited from lists of Medicare beneficiaries in Pittsburgh, PA, and Memphis, TN, in 1997–1998 (N = 3 075). Participants were ages 70–79 years and free from baseline difficulty walking ¼ mile and climbing 10 steps. The study was reviewed and approved by Institutional Review Boards at the respective sites, and participants provided informed consent before any study procedures were carried out.

Biological Age

To keep this work clinically applicable, we used a multi-biomarker algorithm comprised of common clinical tests to quantify BA. This algorithm (21) is an abbreviated version of the model established using data from the US National Health and Nutrition Survey (NHANES) (8,22,23) and was constituted by 8 biomarkers assessed at Health ABC study baseline: C-reactive protein (mg/dL), serum creatinine (mg/dL), plasma total cholesterol (mg/dL), forced expiratory volume (mL), hemoglobin A1c (%), systolic blood pressure (mmHg), albumin (g/dL), and alkaline phosphatase (U/L). The approach is modified from Klemera and Doubal's (9), which performed best for mortality prediction when tested against other BA algorithms within the NHANES-III study (1).

Outcomes

Cognition

Global cognition was assessed using the Modified Mini-Mental State Examination (3MS) (25), and executive function was assessed using the Digit Symbol Substitution Test (DSST). The 3MS was completed at Years 1, 3, 5, 8, and 10, and the DSST was completed at Years 1, 5, 8, and 10. Higher scores indicate better cognitive function, with meaningful change identified as a 5-point decline on 3MS and a 3- to 6-point decline for DSST (26,27).

Frailty

We used the Scale of Aging Vigor in Epidemiology (SAVE), a 10-point frailty score (0 = no frailty, 10 = frailest) developed by Sanders et al. (28) based on a modified Fried frailty phenotype (FFP) (29,30) and previously evaluated within the Health ABC cohort (31). It includes an assessment of weight change in the past year, physical activity, gait speed, grip strength, and usual energy level. We calculated frailty for each participant at Years 2, 4, 6, 8, and 10. Year 2 was used as the baseline for frailty to allow for the calculation of weight change in the past year. The SAVE extends the well-performing end of the FFP scale such that milder changes may be more precisely detected in generally well-functioning older adults, making it a well-tailored measure of frailty in Health ABC participants (28). The SAVE score is associated with a greater disease burden in older adults (28). Detailed methods are provided in the Supplementary Methods and Supplementary Table 1. No estimates of meaningful change on the SAVE have been published. Given that SAVE is an extended version of the FFP (multiplied by 2), we considered the equivalent meaningful change on the FFP multiplied by 2. Estimates for a small change range from 0.20 to 0.50 (ie, 2 × [0.10 – 0.25]), and estimates for a large change range from 1.22 to 1.24 (ie, 2 × [0.61 – 0.62]) (32).

Demographics and Comorbidities

Education was self-reported and categorized as ≤high school (HS) or >HS. Date of birth (used to calculate CA), sex, and race were self-reported and based on Health Care Financing Administration (HCFA; now the Centers for Medicare and Medicaid Services) data collected by HCFA from the Social Security Administration and used by Health ABC. Separate data on gender were not collected.

The Center for Epidemiologic Studies Depression scale (CES-D; range 0–60) was used to quantify depressive symptoms, with a cutoff of ≥10 indicating the presence of significant depressive symptoms (33,34). Individual comorbidities were self-reported, and if any comorbidity in the following specific categories was present, that category was coded as present (vs absent): cardiovascular = myocardial infarction, congestive heart failure, angina pectoris, coronary bypass/coronary artery bypass grafting; cerebrovascular = transient ischemic attack, stroke/cerebrovascular accident; vascular = hypertension, diabetes mellitus, current smoker; physical = arthritis, osteoporosis; respiratory = asthma, chronic obstructive pulmonary disease, emphysema, chronic bronchitis; and cancer = any cancer.

Statistical Analysis

Creation of BA–CA groups

To keep our primary predictor variable and models easily interpretable, and because no biologically based clinical cut-points of BA and CA exist for this age range, we created 4 BA–CA groups based on median splits of BA and CA calculated in all participants with data on BA and CA (N = 2 776). "Younger" defines an age below the median BA and CA, and "older" above or equal to the median age. Two groups were concordant on BA and CA (Young group = younger BA, younger CA; Old group = older BA, older CA), and 2 groups were discordant (Prematurely Aging group = older BA, younger CA; Resilient group = younger BA, older CA).

Descriptive statistics

Using the analytic data set with the largest sample size (3MS), baseline demographics, comorbidities, and outcomes were examined across BA–CA groups and compared using analyses of variance for continuous variables and chi-square tests for categorical variables. We also present descriptive statistics by high versus low BA, high versus low CA, sex, and race.

Validation of BA–CA groups with mortality

We sought to validate the BA–CA groups by confirming their association with mortality. We tested associations via Cox proportional hazards regression using dropout and death at the Year 10 visit. The survival time was calculated as the number of years from the Year 1 visit to death or was censored at the last known visit. The proportional

hazards assumption was examined by visual assessments and Schoenfeld tests. The Young group was the reference group, and we calculated hazard ratios and 95% confidence intervals with and without accounting for competing risks by incorporating the cause-specific attrition due to dropout and death. For each of these models, we tested the inclusion of demographics (sex, race, and education), and the final model was selected based on the backward selection of covariates with $p < .05$.

Primary analyses

We first wanted to confirm that BA was associated with our outcomes independent of CA, so we used linear mixed models (LMMs) to assess the relationship of continuous BA with 3MS, DSST, and frailty over time, adjusting for continuous CA. Then we used joint models to assess the relationship between the BA–CA groups and 3MS, DSST, and frailty over time. This approach jointly estimates a longitudinal submodel—an LMM—and a survival submodel with a shared random effect which accounts for individual-level common causes of dropout/death and changes in cognitive and physical function (35,36). Joint models provide more accurate estimates of cognitive decline than other longitudinal models (including LMM alone) under a variety of relationship structures and are more robust to survival bias (37). The estimation method in this approach is the maximum likelihood considering a joint distribution of the observed outcome (38). For the longitudinal submodel, based on comparisons of the Akaike Information Criterion and Bayesian Information Criterion, random intercepts and slopes improved model fit for all 3 outcomes; therefore, all models incorporate these parameters. For the survival submodel, a time-dependent relative risk model is assumed in which the log baseline risk function is approximated using B-splines. The required integrals are approximated using the (pseudo) adaptive Gauss–Hermite rule. The survival submodels accounted for cause-specific attrition due to both dropout and death. The Young group was the reference group. Base models (Model 1) of cognitive outcomes and frailty were adjusted for education; Model 2 was further adjusted for race and sex. To account for change over time, interactions of BA–CA group and all covariates with time were included if $p < .10$. We tested the 3-way interaction of BA–CA group with race and sex and included any interactions with $p < .10$.

This investigation examined the relationship between BA–CA group and new cognitive decline or frailty. As such, participants with severe impairment in the outcome measure at baseline were excluded. Because no participants exhibited notable global cognitive impairment at baseline (defined as a 3MS < 80), no participants were excluded based on this criterion. For the frailty models, those participants who were extremely frail at baseline (scoring in the highest standard deviation—a score of 9 or 10) were excluded. Thus, the analytic sample sizes for the analyses of participants with complete data for BA–CA group and each outcome were $N = 2\,458$ for 3MS, $N = 2\,450$ for DSST, and $N = 2\,151$ for frailty. For each BA–CA group or BA–CA group × time interaction relative to the young group, results are presented as coefficients, standard errors (*SE*), and *p* values. We present additional pairwise comparisons and both unadjusted and multiple comparisons adjusted *p* values using a Šidák correction. If BA is a meaningful indicator of cognitive and physical outcomes, then differences in cross-sectional and longitudinal analyses should be observed when comparing the Prematurely Aging versus Young groups and the Resilient versus Old groups.

Alpha for primary analyses was set at 0.05, and statistical analyses were carried out in SAS 9.4 (SAS Institute, Cary, NC) (39) and R version 4.1.1 (The R Foundation, Indianapolis, IN) (40). Joint modeling was carried out in R using package JM (41).

Results

Descriptive Statistics

Despite a CA that ranged from 70 to 79 by design, BA ranged from 50.0 to 115.5; median BA and CA were 70.0 and 74.0, respectively. Baseline characteristics by low versus high BA and low versus high CA are presented in Supplementary Table 2. Compared to those with high BA, those with low BA were significantly more likely to have younger CA, be male, White, and more highly educated, and have fewer comorbidities and better cognition and frailty scores (Supplementary Table 2). A similar pattern emerged with CA, although the low and high CA groups did not significantly differ in education nor in as many comorbidities (Supplementary Table 2).

Baseline characteristics for the full sample and by BA–CA group are presented in Table 1. Overall, the sample was 52.1% female, 64.6% White, with a mean (*SD*) CA of 73.5 (2.8) years (Table 1). At baseline, the Prematurely Aging group had a BA about 12 years older than the Young group despite having a similar CA and the Resilient group had a BA about 12 years younger than the Old group despite having a similar CA. The BA–CA groups differed in sex, race, education, and vascular, physical, and respiratory comorbidities (all *p*'s < .01; Table 1). The Prematurely Aging group consisted of more Black and female participants with lower education levels and more vascular and respiratory comorbidities while the Resilient group consisted of more White and male participants with greater education and fewer vascular and respiratory comorbidities. Baseline characteristics by race and sex are presented in Supplementary Table 3 and show that Black participants (vs White) and female participants (vs male) had older BA, and as such were likelier to be classified in the Prematurely Aging and Old groups.

Validation of BA–CA Groups With Mortality

Mortality rates increased as a function of BA–CA group, being the lowest in the Young group and the highest in the Old group ($p < .0001$); dropout was minimal (Table 1). These differences were observed in Cox proportional hazards models; results from the models using the 3MS analytic sample are shown in Supplementary Table 4. Results in the DSST and frailty samples were similar (not shown).

Cognition

Modified Mini-Mental State Examination

In an LMM examining the association of BA with 3MS adjusting for CA, at baseline, each 1-year older BA was associated with 0.11 points lower 3MS score (*SE*: 0.01; $p < .0001$). CA was not significantly associated with 3MS (β (*SE*): −0.002 (0.04); $p = .96$) in this model, while it was in a model without BA (β (*SE*): −0.08 (0.04); $p = .03$). Those with greater BA did not decline more rapidly over time (BA × time interaction $p = .41$), while those with greater CA did (CA × time interaction $p < .0001$).

Table 1. Baseline Participant Characteristics by Biological Age–Chronological Age Groups

Characteristic	Full Sample, *N* = 2 458	Young Group, *n* = 787 (32.02%)	Prematurely Aging Group, *n* = 518 (21.07%)	Old Group, *n* = 666 (27.10%)	Resilient Group, *n* = 487 (19.81%)	*p*-value
Demographics						
Chronological age	73.53 (2.83)	71.18 (1.28)	71.8 (1.18)	76.24 (1.71)	75.91 (1.57)	<.0001
Biological age	70.13 (7.82)	63.80 (4.23)	75.77 (4.93)	76.99 (6.00)	64.95 (3.86)	<.0001
Female sex	1 280 (52.07)	365 (46.38)	352 (67.95)	399 (59.91)	164 (33.68)	<.0001
White race	1 587 (64.56)	565 (71.79)	237 (45.75)	380 (57.06)	405 (83.16)	<.0001
Education ≤ HS	1 315 (53.63)	386 (49.11)	322 (62.40)	404 (60.84)	203 (41.77)	<.0001
Depression						
CES-D score	4.46 (5.06)	4.32 (5.36)	4.74 (5.26)	4.47 (4.54)	4.41 (4.94)	.5804
# CES-D ≥ 10 (%)	271 (13.11)	82 (11.65)	65 (15.05)	69 (13.40)	55 (13.22)	.4259
Medical comorbidities						
Vascular	1 372 (58.28)	387 (51.12)	359 (72.38)	432 (67.50)	194 (42.08)	<.0001
Physical	1 349 (57.31)	395 (52.25)	292 (58.99)	391 (60.90)	271 (58.74)	.0065
Respiratory	416 (17.88)	114 (15.24)	116 (23.67)	126 (19.94)	60 (13.13)	<.0001
Cardiovascular	522 (21.83)	151 (19.71)	113 (22.16)	164 (25.23)	94 (20.22)	.0670
Cerebrovascular	177 (7.22)	45 (5.73)	37 (7.17)	60 (9.04)	35 (7.20)	.1184
Cancer	114 (4.97)	43 (5.81)	14 (2.94)	30 (4.82)	27 (5.92)	.1039
Baseline outcomes						
3MS score	92.43 (4.99)	93.44 (4.75)	91.63 (5.06)	91.57 (5.09)	92.80 (4.82)	<.0001
DSST score	37.96 (13.15)	40.89 (12.77)	36.70 (13.06)	35.18 (13.24)	38.35 (12.75)	<.0001
Frailty score*	4.47 (1.86)	3.95 (1.80)	4.56 (1.76)	5.09 (1.85)	4.52 (1.84)	<.0001
Mortality by end of study, # (%)	623 (25.35)	120 (15.25)	152 (29.34)	216 (32.43)	135 (27.72)	<.0001
Dropout by end of study, #(%)	10 (0.41)	7(0.89)	2(0.39)	1(0.15)	0(0.00)	<.0001

Notes: *N* = 2 458. 3MS = Modified Mini-Mental State Examination; CES-D = Center for Epidemiologic Studies—Depression scale; DSST = Digit Symbol Substitution Test; HS = high school.
*For frailty variables, Year 2 was defined as the "baseline" visit.

In a joint model adjusting for education and the education × time interaction, there were group differences observed in mean 3MS at baseline (Model 1, Table 2). In the pairwise comparisons of interest, the Prematurely Aging group scored significantly worse than the Young group (1.11 points lower, Table 2), but the Resilient group did not perform significantly better than the Old group (Model 1 β (*SE*): 0.45 (0.43) points higher, $p = .31$, Šidák corrected $p = .88$). The mean yearly decline in 3MS across participants was about 0.40 points per year, with a slope change of an additional loss of 0.22 points at Year 5 (Year 5 × time interaction $p = .004$; Table 2). The Prematurely Aging group declined at about the same pace as the Young ($p = .92$), and the Resilient declined at about the same rate as the Old (β (*SE*): 0.08 (0.11) points difference, $p = .45$, Šidák corrected $p = .97$). This relationship in change over time by group is also observed in Figure 1. The Prematurely Aging and Young groups did not decline by a meaningful amount over follow-up, while the Resilient and Old groups did (Supplementary Table 5).

Further adjustment for race, sex, education, and interaction terms where $p < .10$ (education × time and race × time interaction terms) did not alter this overall pattern of results (Model 2, Table 2).

Digit Symbol Substitution Test

In an LMM examining the association of BA with DSST adjusting for CA, at baseline, each 1-year older BA was associated with 0.23 points lower DSST score (*SE*: 0.03; $p < .0001$), and each 1-year older CA was associated with 0.45 points lower DSST score (*SE*: 0.10; $p < .0001$). Those with greater BA did not decline more rapidly over time (BA × time interaction $p = .18$), while those with greater CA did (CA × time interaction $p < .0001$).

In the joint model adjusting for education and the education × time interaction, there were group differences in mean executive function at baseline. In the pairwise comparisons of interest, the Prematurely Aging group scored significantly lower than the Young group (2.92 points lower; Model 1, Table 3), but the Resilient group did not perform significantly differently from the Old group (Model 1 β (*SE*): 1.26 (1.10) points higher, $p = .25$, Šidák corrected $p = .83$). Across all participants, the mean decline on DSST was about 0.53 points per year. The Prematurely Aging group declined at about the same rate as the Young group ($p = .16$, Table 3), and the Resilient group declined at about the same pace as the Old group (Model 1 β (*SE*): 0.14 (0.12) points difference, $p = .26$, Šidák corrected $p = .83$). Over the 10 years of follow-up, all groups declined by a meaningful amount (Supplementary Table 5 and Figure 1).

Table 2. Association Between Biological Age–Chronological Age Groups and Global Cognition Measured by the Modified Mini-Mental State Examination

	Model 1				Model 2			
	β	*SE*	*p*-value	Šidák corrected *p*-value	β	*SE*	*p*-value	Šidák corrected *p*-value
BA–CA group								
Young group	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Prematurely Aging group	−1.11	0.27	<.0001	.0002	−0.95	.26	.0003	.002
Old group	−0.90	0.25	.0003	.002	−0.88	.24	.0002	.001
Resilient group	−0.45	0.27	.10	.46	−0.71	.26	.006	.03
Time	−0.40	0.07	<.0001	—	−0.49	.08	<.0001	—
Year 5 × time	−0.22	0.08	.004	—	−0.19	.08	.01	—
BA–CA Group × time								
Young group × time	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Prematurely Aging group × time	0.007	0.07	.92	>.99	0.05	0.07	.46	.98
Old group × time	−0.33	0.07	<.0001	.0002	−0.30	0.07	<.0001	.0002
Resilient group × time	−0.24	0.07	.0004	.002	−0.21	0.07	.002	.01

Notes: $N = 2\,452$ with complete data on BA–CA group, Modified Mini-Mental State examination, and covariates. Results are coefficients and standard errors from the longitudinal submodel of the joint model accounting for attrition due to dropout and death. Model 1 is adjusted for education and an education × time interaction. Model 2 is adjusted for race, sex, education, and interaction terms for education × time and race × time. A Year 5 × time interaction was included because the slope of the Modified Mini-Mental State score over time steepened at Year 5. BA = biological age; CA = chronological age; *SE* = standard error.

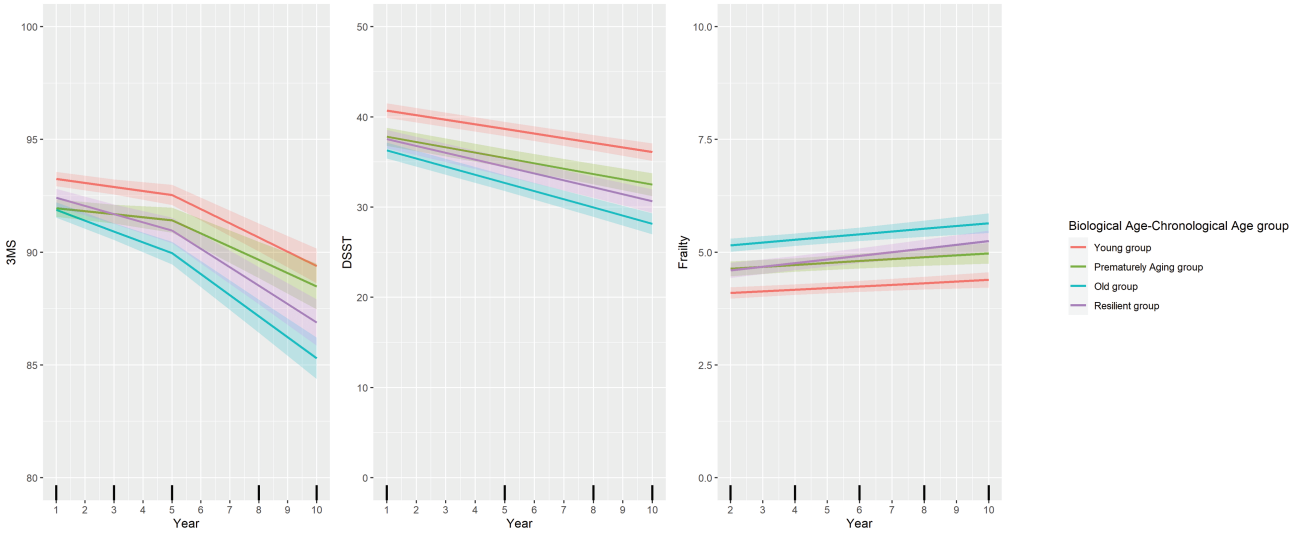

Figure 1. Global cognition (by Modified Mini-Mental State Examination), executive function (by Digit Symbol Substitution Test), and frailty by biological age–chronological age group. 3MS = Modified Mini-Mental State Examination; DSST = Digit Symbol Substitution Test. Years on *x*-axis with bold tick marks are years with visit data.

Model 2 was further adjusted for race, sex, and interaction terms where $p < .10$ (race × time and the 3-way interaction of race × sex × BA–CA group along with component 2-way interactions). This attenuated the baseline difference between the Prematurely Aging and Young groups (Table 3).

Frailty

In an LMM examining the association of BA with frailty adjusting for CA, at baseline, each 1-year older BA was associated with 0.04 points greater frailty score (*SE*: 0.006; $p < .0001$), and each 1-year older CA was associated with 0.09 points greater frailty score (*SE*: 0.02; $p < .0001$). Those with greater BA did not worsen more rapidly over time (BA × time interaction $p = .43$), while those with greater CA did (CA × time interaction $p = .002$).

In a joint model adjusted for education, there were group differences in mean baseline frailty burden. In the pairwise comparisons of interest, the Prematurely Aging group was significantly frailer than the Young group (0.50 points higher; Model 1, Table 4), and the Resilient group was significantly less frail than the Old group (0.59 (0.20) points lower; Model 1 $p = .003$, Šidák corrected $p = .02$). Frailty score across all participants increased each year (0.04 points, $p = .0001$; Table 4). Frailty burden increased at about the same rate in the Prematurely Aging and Young groups ($p = .40$, Table 4), and in the Resilient and Old groups (Model 1 β (*SE*): 0.02 (0.03) points difference, $p = .59$, Šidák corrected $p > .99$). Over the 10 years of follow-up, all groups worsened in line with a small, but meaningful increase in frailty burden (Supplementary Table 5 and Figure 1).

Table 3. Association Between Biological Age–Chronological Age Groups and Executive Function Measured by the Digit Symbol Substitution Test

	Model 1				Model 2			
	β	*SE*	*p*-value	Šidák corrected *p*-value	β	*SE*	*p*-value	Šidák corrected *p*-value
BA–CA group								
Young group	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Prematurely Aging group	−2.92	0.67	<.0001	.0002	−1.20	1.54	.44	.97
Old group	−4.11	0.63	<.0001	.0002	−2.64	1.48	.08	.37
Resilient group	−2.86	0.68	<.0001	.0002	−2.29	1.83	.21	.76
Time	−0.53	0.05	<.0001	—	−0.47	0.07	<.0001	—
BA–CA group × time								
Young group × time	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Prematurely Aging group × time	−0.11	0.08	.16	.64	−0.13	0.08	.10	.47
Old group × time	−0.42	0.07	<.0001	.0002	−0.43	0.07	<.0001	.0002
Resilient group × time	−0.28	0.08	.0004	.002	−0.26	0.09	.0008	.005

Notes: *N* = 2 448 with complete data on BA–CA group, Digit Symbol Substitution Test, and covariates. Results are coefficients and standard errors from the longitudinal submodel of the joint model accounting for attrition due to dropout and death. Model 1 is adjusted for education and an education × time interaction. Model 2 is adjusted for race, sex, education, and interaction terms for race × time, race × BA–CA group interaction, sex × BA–CA group, race × sex, race × sex × BA–CA group. BA = biological age; CA = chronological age; *SE* = standard error.

Table 4. Association Between Biological Age–Chronological Age Groups and Frailty

	Model 1				Model 2			
	β	*SE*	*p*-value	Šidák corrected *p*-value	β	*SE*	*p*-value	Šidák corrected *p*-value
BA–CA group								
Young group	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Prematurely Aging group	0.50	0.12	.0001	.0006	0.53	0.13	<.0001	.0002
Old group	0.99	0.12	<.0001	.0002	1.00	0.12	<.0001	.0002
Resilient group	0.40	0.12	.001	.008	0.41	0.13	.001	.007
Time	0.04	0.01	.0001	—	0.09	0.02	<.0001	—
BA–CA group × time								
Young group × time	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Prematurely Aging group × time	0.02	0.02	0.40	.95	0.01	0.02	0.54	>.99
Old group × time	0.03	0.02	.06	.31	0.03	0.02	.08	0.40
Resilient group × time	0.05	0.02	.007	0.04	0.05	0.02	.01	06

Notes: *N* = 2 146 with complete data on BA–CA group, frailty, and covariates. Results are coefficients and standard errors from the longitudinal submodel of the joint model accounting for attrition due to dropout and death. Model 1 is adjusted for education. Model 2 is adjusted for race, sex, and interactions for race × sex, race × time, and sex × time. BA = biological age; CA = chronological age; *SE* = standard error.

Further adjusting for race, sex, and interactions with $p < .10$ (race × sex, race × time, and sex × time) did not alter these results (Model 2, Table 4).

Discussion

Examining both BA and CA together may give more complete information about function. Comparing groups with the same CA but different BAs gives information about the importance of BA at both younger and older CAs, and our key results suggest that BA is associated with baseline cognition at only younger CA but is associated with baseline physical function at both younger and older CA. Groups with the same CA but differing BAs did not differ on cognitive and physical change over time, suggesting that CA is a more meaningful marker of changes in cognition and physical function over time in this age range. This extends our own previous work showing that BA and CA were associated with 3MS cross-sectionally, but BA was not associated with 3MS over time, while CA was (21). These results agree and together support the consideration of temporality in understanding factors of premature and resilient aging.

BA and Where Participants Start

BA was associated with all cognitive and frailty measures at baseline, independent of CA. Interestingly, the association of CA with baseline 3MS was not independent of BA. These results suggest that getting a complete picture of older adults' risk of poor cognition and frailty requires integrating information about both BA and CA.

Younger BA was associated with better baseline global cognition (3MS) and executive performance (DSST) for those with younger (mean, ~71) but not older (mean, ~76) CA. Though our study did not include younger age groups, and thus was unable to test this empirically, the relevance of BA up to, but not after, the age of 71 suggests that this measure of BA may be more important at younger ages, especially before

the eighth decade, and potentially much earlier, for example, in the third and fourth decades of life (8). Younger adults with a prematurely old BA may represent a higher risk group for age-related disease. They may benefit most from early interventions, prior to significant disease onset and accumulated multisystem dysregulation (2), and should be prioritized for interventions targeting cognition and frailty.

Previous research has also found support for an older BA being associated with worse cognition, although this was not CA dependent (12,15,17). The results in our study might differ for a few reasons. First, 2 of the 3 cited studies included participants with a younger mean CA at the time when BA was measured compared to ours (mean CAs of 50 and 68 in the other studies vs 74 in ours). As such, the effect of BA on cognition might have been driven by these younger CAs. Second, few demographic variables were reported in the other studies, but sex, race/ethnicity, and potentially other characteristics differed across studies. Sample differences in effect modifiers could alter the relationship between BA–CA and cognition, and these should be reported in future research (42). Third, each study used different measures of cognitive function; these may be differentially related to BA. Finally, of the studies cited here, 1 was cross-sectional, and the other 2 did not specifically account for attrition. Our study used joint modeling on data across 10 years of follow-up, which accounts for potential differential attrition due to dropout or death and more comprehensively minimizes this bias.

Younger BA was associated with less baseline frailty for both those with younger and older CA, and these results persisted after adjusting for education, sex, race, and corresponding interactions. A relationship between older BA and worse physical function is well supported in the literature (12,15,18). Why would BA be associated with baseline cognition in an age-dependent way, but with frailty in an age-independent way? First, our results are consistent with previous work suggesting that organ systems can age at different rates (3,43). Our measure of BA used biomarkers from easily accessible clinical tests reflecting many biological systems, but not directly relating to the central nervous system, although our previous work has shown this BA measure was associated with higher depressive symptoms and greater risk of developing elevated depressive symptoms over time (21). Further supporting this, Verschoor et al. (16) found that Klemara Doubal BA, while associated with multiple body systems, was not associated with neurological or musculoskeletal systems. Taken together, these findings suggest that *brain* aging may occur at a different rate than other systems. Second, someone with an older BA but a younger CA (prematurely aging) may be in worse health across multiple body systems compared to another person who survives an older CA with a concordant or younger BA. This may result in more consistent biological aging across body systems (including the brain) in prematurely aging people, but more disparate biological aging across systems for those with an older CA and concordant or younger BA. Future work on biomarker indices specific to brain aging may enable more insight into cognitive aging.

BA and How Participants Change Over Time

At similar CA, the rate of decline did not differ by BA for cognitive function or frailty. While a younger BA may protect against poorer cognitive and physical performance up to around age 74, it doesn't appear to alter functional decline over the next decade of life. This suggests that BA may have beneficial effects earlier in life and that CA is more important than BA for both change in cognition and frailty over time. Furthermore, given that these changes did not vary in the discordant versus concordant group comparisons, the baseline benefits of younger BA we observed at younger CA are maintained over time. Similar patterns of association with better baseline cognitive function but not rate of cognitive decline have been noted for other factors such as educational attainment (44). The relationship between the rate of physical function decline and BA requires additional research. We found that change in frailty was more strongly related to CA than to BA, while the Singapore Longitudinal Aging Study (SLAS-2) has reported that BA was associated with incident frailty over 8 years of follow-up among Chinese Singaporean older adults. In their subgroup ≥71 years of age, this association was independent of CA (18). The study included an age range from 55 to 94 and was 63% female (vs our sample, 52%). Our differing results may be due to differing participant characteristics or differing analytic approaches, as the SLAS-2 did not account for attrition due to dropout and death.

Meaningful Change

A mean difference in CA of 5 years in the older versus younger CA groups appears small, so how meaningful are our results? The 9-year CA range represented in this study rather remarkably maps onto a 65.5-year BA range. Furthermore, these BA and CA differences capture important differences in comorbidities and function in the eighth decade of life. All BA–CA groups declined a meaningful amount across the 10-year follow-up period on all assessments, with 2 exceptions; interestingly, the Young and Prematurely Aging groups did not meet the threshold of a meaningful change over time on the 3MS. With regard to baseline group differences, the Prematurely Aging group scored just under 3 points lower than the Young group on the DSST, a cross-sectional group difference that nearly rises to the level of meaningful change. This is important to consider, as our results suggest that not only is BA associated with a statistically significant difference in DSST among those with younger CA, but this difference in executive functioning borders on clinically meaningful for older adults. This same pattern—a cross-sectional group difference that rises to the level of meaningful change—was also noted when comparing frailty burden across the discordant groups (Prematurely Aging vs Young and Resilient vs Old).

Comorbidities, Race, and Sex

Multiple medical comorbidities were associated with group differences. This was expected as BA was calculated using clinical metrics strongly correlated with comorbid disease, such as inflammatory markers and arthritic pain. Even so, these medical comorbidities are important to consider as potential clinical indicators or drivers of advanced aging, as well as systems of disease that directly impact an older adult's lived experience. Interestingly, the Resilient group had a lower burden of both vascular and respiratory comorbidities than even the Young group, identifying these 2 systems as potentially paramount to maintaining resiliency, and thus promoting longer cognitive and physical independence. Given the long-term sequelae of coronavirus disease 2019 (COVID-19), these comorbidities may be critical to consider in aging research moving forward.

We found that Black participants had an older BA and a greater burden of vascular and respiratory comorbidities

than White participants. Additionally, female participants had an older BA and reported greater depressive symptoms and physical comorbidities than male participants. These results are consistent with other research showing that Black participants may present with more severe morbidities (45), a finding that has been emphasized during the COVID-19 pandemic (46). It has also been consistently reported that women have lower mortality but greater morbidity than men, particularly at older ages (14,19). These results, and our own, likely in part reflect differential survival for selection into the study with men dying younger (eg, of cardiovascular disease) than women, and thus only the most robust men surviving to participate in studies of aging. Furthermore, there is a body of evidence supporting a role of social determinants of health and gender/sex differences in biological aging, especially with cognitive outcomes (47,48). As our primary goal here did not involve evaluation of gender/sex and race differences, we did not measure factors such as racism, sexism, and other gender-related factors, and future work is needed to study sociocultural factors that may be contributing to these differences. Social determinants of health such as education, socioeconomic status, and material and social resources, as well as adverse life events, have been linked to BA (15,47). Accounting for such factors can enhance external validity and clinical value of BA measures, and as such they are a promising area for continued BA research and can be incorporated into BA conceptual frameworks as social hallmarks of aging (47).

Strengths and Limitations

Strengths of the current study include a large community-based sample with detailed participant characterization that allowed for the construction of BA and for adjusting for confounders. Our use of joint models enabled us to account for attrition over time due to both dropout and death, thereby providing more accurate estimates. Finally, the longitudinal design with 10 years of follow-up enabled us to look at rates of decline, a metric with high clinical relevance.

There are several limitations of this work that should be kept in mind. First, we chose variables and modeling approaches that prioritized ease of use and interpretability to maximize accessibility to clinicians. However, other investigators with different goals may make different choices. For example, we used Klemera–Doubal BA which is strongly predictive of mortality and easy for clinicians and researchers to apply given its reliance on commonly used clinical tests (1), but it is only 1 approach to calculating BA. It is possible that this calculation of BA does not capture all important dimensions. We dichotomized the BA and CA variables, which are easy to interpret, while other investigators may prefer the greater power and accuracy that comes with continuous variables. We chose to address potential differences in age associations by sex and race in our modeling by including the BA–CA × sex × race and any 2-way interactions with $p < .10$ in our models; we also tested interactions with time. Other researchers may choose to calculate sex- and race-specific BA and CA medians. Second, it is possible that BA does not perform as well at extreme CAs; future research to disentangle this possibility would be of interest to the field going forward. Third, the biomarkers used to calculate BA in the current study were collected only once, at baseline. However, biological indices of aging change over time (pace of biological aging) and as such future studies should account for these changes. Fourth, this study recruited largely healthy older adult volunteers and recruitment occurred in 2 cities, both in the United States. Excellent work has been done previously considering BA in other cultures, countries, and settings, and continued work among various older adult populations is needed. Finally, although we refer to the Young group as concordant, they have a notably younger BA than CA (BA = 63.8 vs CA = 71.2 years), which may contribute to their good performance. Future work should consider purposefully matching such a concordant young group more closely on BA and CA.

Future Directions

This work lends itself to a multitude of additional questions. As mentioned above, there is evidence that different organ systems may age at different rates. Does the age of certain organs matter more than others to the overall well-being of a person? What factors drive differential organ aging? Further investigation into these and other questions can elucidate various mechanisms of aging and may highlight personalized treatment targets. The scope and sample considerations of Population Neuroscience (49) in conversation with the granular expertise of basic science have the potential to support precision public health across communities (50). To this end, more research is needed into the social factors that contribute to biological aging and diverse, representative samples should be rigorously considered.

Animal models suggest that BA is inherently modifiable; researchers aim to have the same impact in humans, with gerotherapeutics trials, such as the Targeting Aging by MEtformin (TAME) trial (51), being designed and run (52). Over the long term, future interventions seeking to improve cognitive and physical function in aging may target BA and use it as a surrogate outcome. Our study suggests that younger CA may represent a critical time for preventive intervention. Future work should more precisely delineate critical time points for maximizing baseline health and consider preventive measures across the life span to promote and support healthy aging most effectively.

Conclusion

Discordant BA and CA identify groups who have greater cognitive and physical functional decline or are more protected than their CA would suggest. This information should be used for risk stratification and future studies to better understand resilient aging.

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

This research was supported by National Institute on Aging (NIA) contracts #N01AG62101, N01AG62103, N01AG62106; NIA grants R01AG028050, K01AG071849, T32AG055381; and National Institute of Nursing Research grant R01NR012459. This research was supported by the University of Pittsburgh Older Americans Independence Center (NIH P30 AG024827). Research content reported

in this publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflict of Interest

None.

Acknowledgments

The authors would like to thank Dr. Andrea L. Metti for support with statistical analyses and neuropsychologist Dr. Beth E. Snitz for helpful conversations surrounding meaningful change on cognitive assessments.

Author Contributions

C.E.S. led study conceptualization, methodology, writing of the original draft, review, and editing and contributed to data curation and formal analysis. C.R. contributed to study conceptualization, funding acquisition, methodology, project administration, and writing review and editing. X.Z. led data curation and formal analysis and contributed to methodology and writing review and editing. B.R.R. contributed to conceptualization, methodology, and writing review and editing. K.R.W. contributed to writing the original draft and review and editing. A.L.R. contributed to conceptualization, methodology, and writing review and editing. K.Y. contributed to conceptualization, funding acquisition, project administration, and writing review and editing. P.J.B. led study conceptualization, data curation, and supervision and contributed to methodology, writing of the original draft, review, and editing.

References

1. Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? *J Gerontol A Biol Sci Med Sci*. 2013;68:667–674. doi:10.1093/gerona/gls233
2. Arbeev KG, Ukraintseva SV, Bagley O, et al. "Physiological dysregulation" as a promising measure of robustness and resilience in studies of aging and a new indicator of preclinical disease. *J Gerontol A Biol Sci Med Sci*. 2019;74:462–468. doi:10.1093/gerona/gly136
3. Li Q, Wang S, Milot E, et al. Homeostatic dysregulation proceeds in parallel in multiple physiological systems. *Aging Cell*. 2015;14:1103–1112. doi:10.1111/acel.12402
4. Liu Z, Kuo PL, Horvath S, Crimmins E, Ferrucci L, Levine M. A new aging measure captures morbidity and mortality risk across diverse subpopulations from NHANES IV: a cohort study. *PLoS Med*. 2018;15:e1002718. doi:10.1371/journal.pmed.1002718
5. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proc Natl Acad Sci USA*. 2001;98:4770–4775. doi:10.1073/pnas.081072698
6. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *Scientific World Journal*. 2001;1:323–336. doi:10.1100/tsw.2001.58
7. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. *CMAJ*. 2011;183:E487–E494. doi:10.1503/cmaj.101271
8. Belsky DW, Caspi A, Houts R, et al. Quantification of biological aging in young adults. *Proc Natl Acad Sci U S A*. 2015;112:E4104–E4110. doi:10.1073/pnas.1506264112
9. Klemera P, Doubal S. A new approach to the concept and computation of biological age. *Mech Ageing Dev*. 2006;127:240–248. doi:10.1016/j.mad.2005.10.004
10. Arosio B, Ferri E, Casati M, Mari D, Vitale G, Cesari M. The Frailty Index in centenarians and their offspring. *Aging Clin Exp Res*. 2019;31:1685–1688. doi:10.1007/s40520-019-01283-7
11. Crimmins EM, Thyagarajan B, Kim JK, Weir D, Faul J. Quest for a summary measure of biological age: the health and retirement study. *GeroScience*. 2021;43:395–408. doi:10.1007/s11357-021-00325-1
12. Gaydosh L, Belsky DW, Glei DA, Goldman N. Testing proposed quantifications of biological aging in Taiwanese older adults. *J Gerontol A Biol Sci Med Sci*. 2020;75:1680–1685. doi:10.1093/gerona/glz223
13. Goggins WB, Woo J, Sham A, Ho SC. Frailty index as a measure of biological age in a Chinese population. *J Gerontol A Biol Sci Med Sci*. 2005;60:1046–1051. doi:10.1093/gerona/60.8.1046
14. Li X, Ploner A, Wang Y, et al. Longitudinal trajectories, correlations and mortality associations of nine biological ages across 20-years follow-up. *Elife*. 2020;9. doi:10.7554/eLife.51507
15. Hastings WJ, Shalev I, Belsky DW. Comparability of biological aging measures in the National Health and Nutrition Examination Study, 1999–2002. *Psychoneuroendocrinology*. 2019;106:171–178. doi:10.1016/j.psyneuen.2019.03.012
16. Verschoor CP, Belsky DW, Ma J, Cohen AA, Griffith LE, Raina P. Comparing biological age estimates using domain-specific measures from the Canadian Longitudinal Study on Aging. *J Gerontol A Biol Sci Med Sci*. 2021;76:187–194. doi:10.1093/gerona/glaa151
17. MacDonald SW, Dixon RA, Cohen AL, Hazlitt JE. Biological age and 12-year cognitive change in older adults: findings from the Victoria Longitudinal Study. *Gerontology*. 2004;50:64–81. doi:10.1159/000075557
18. Zhong X, Lu Y, Gao Q, et al. Estimating biological age in the Singapore Longitudinal Aging Study. *J Gerontol A Biol Sci Med Sci*. 2020;75:1913–1920. doi:10.1093/gerona/glz146
19. Mitnitski A, Collerton J, Martin-Ruiz C, et al. Age-related frailty and its association with biological markers of ageing. *BMC Med*. 2015;13:161. doi:10.1186/s12916-015-0400-x
20. Graf GH, Crowe CL, Kothari M, et al. Testing Black-White disparities in biological aging in older adults in the United States: analysis of DNA-methylation and blood-chemistry methods. *Am J Epidemiol*. 2021;191:613–625. doi:10.1093/aje/kwab281
21. Brown PJ, Wall MM, Chen C, et al. Biological age, not chronological age, is associated with late-life depression. *J Gerontol A Biol Sci Med Sci*. 2018;73:1370–1376. doi:10.1093/gerona/glx162
22. Gruenewald TL, Seeman TE, Ryff CD, Karlamangla AS, Singer BH. Combinations of biomarkers predictive of later life mortality. *Proc Natl Acad Sci U S A*. 2006;103:14158–14163. doi:10.1073/pnas.0606215103
23. Cohen AA, Milot E, Li Q, et al. Detection of a novel, integrative aging process suggests complex physiological integration. *PLoS One*. 2015;10:e0116489. doi:10.1371/journal.pone.0116489
24. Newman AB, Haggerty CL, Kritchevsky SB, Nevitt MC, Simonsick EM; Health ABC Collaborative Research Group. Walking performance and cardiovascular response: associations with age and morbidity—the Health, Aging and Body Composition Study. *J Gerontol A Biol Sci Med Sci*. 2003;58:715–720. doi:10.1093/gerona/58.8.m715
25. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *J Clin Psychiatry*. 1987;48:314–318.
26. Andrew MK, Rockwood K. A five-point change in Modified Mini-Mental State Examination was clinically meaningful in community-dwelling elderly people. *J Clin Epidemiol*. 2008;61:827–831. doi:10.1016/j.jclinepi.2007.10.022
27. Jehu DA, Davis JC, Madden K, Parmar N, Liu-Ambrose T. Minimal clinically important difference of executive function performance in older adults who fall: a secondary analysis of a randomized controlled trial. *Gerontology*. 2021;68:771–779. doi:10.1159/000518939

28. Sanders JL, Boudreau RM, Fried LP, Walston JD, Harris TB, Newman AB. Measurement of organ structure and function enhances understanding of the physiological basis of frailty: the Cardiovascular Health Study. *J Am Geriatr Soc*. 2011;59:1581–1588. doi:10.1111/j.1532-5415.2011.03557.x
29. Fried LP, Tangen CM, Walston J, et al.; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156. doi:10.1093/gerona/56.3.m146
30. Walston J, McBurnie MA, Newman A, et al.; Cardiovascular Health Study. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. *Arch Intern Med*. 2002;162:2333–2341. doi:10.1001/archinte.162.20.2333
31. Wu C, Li YX, Marron MM, Odden MC, Newman AB, Sanders JL. Quantifying and classifying physical resilience among older adults: the Health, Aging, and Body Composition Study. *J Gerontol A Biol Sci Med Sci*. 2020;75:1960–1966. doi:10.1093/gerona/glz247
32. Jang IY, Jung HW, Lee HY, Park H, Lee E, Kim DH. Evaluation of clinically meaningful changes in measures of frailty. *J Gerontol A Biol Sci Med Sci*. 2020;75:1143–1147. doi:10.1093/gerona/glaa003
33. Meeks TW, Vahia IV, Lavretsky H, Kulkarni G, Jeste DV. A tune in "a minor" can "b major": a review of epidemiology, illness course, and public health implications of subthreshold depression in older adults. *J Affect Disord*. 2011;129:126–142. doi:10.1016/j.jad.2010.09.015
34. Brown PJ, Roose SP, Fieo R, et al. Frailty and depression in older adults: a high-risk clinical population. *Am J Geriatr Psychiatry*. 2014;22:1083–1095. doi:10.1016/j.jagp.2013.04.010
35. Rouanet A, Helmer C, Dartigues JF, Jacqmin-Gadda H. Interpretation of mixed models and marginal models with cohort attrition due to death and drop-out. *Stat Methods Med Res*. 2019;28:343–356. doi:10.1177/0962280217723675
36. Griswold ME, Talluri R, Zhu X, et al. Reflection on modern methods: shared-parameter models for longitudinal studies with missing data. *Int J Epidemiol*. 2021;50:1384–1393. doi:10.1093/ije/dyab086
37. Davis-Plourde KL, Mayeda ER, Lodi S, et al. Joint models for estimating determinants of cognitive decline in the presence of survival bias. *Epidemiology*. 2022;33:362–371. doi:10.1097/EDE.0000000000001472
38. Teixeira L, Sousa I, Rodrigues A, Mendonça D. Joint modelling of longitudinal and competing risks data in clinical research. *Revstat Stat J*. 2019;17:245–264. doi:10.57805/revstat.v17i2.267
39. SAS Institute. *The SAS System for Windows*. SAS Institute; 2013.
40. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2018.
41. Rizopoulos D. JM: an R package for the joint modelling of longitudinal and time-to-event data. *J Stat Softw*. 2010;35:1–33. doi:10.18637/jss.v035.i09
42. Cole SR, Stuart EA. Generalizing evidence from randomized clinical trials to target populations: the ACTG 320 trial. *Am J Epidemiol*. 2010;172:107–115. doi:10.1093/aje/kwq084
43. Rando TA, Wyss-Coray T. Asynchronous, contagious and digital aging. *Nat Aging*. 2021;1:29–35. doi:10.1038/s43587-020-00015-1
44. Lövdén M, Fratiglioni L, Glymour MM, Lindenberger U, Tucker-Drob EM. Education and cognitive functioning across the life span. *Psychol Sci Public Interest*. 2020;21:6–41. doi:10.1177/1529100620920576
45. Javed Z, Haisum Maqsood M, Yahya T, et al. Race, racism, and cardiovascular health: applying a social determinants of health framework to racial/ethnic disparities in cardiovascular disease. *Circ Cardiovasc Qual Outcomes*. 2022;15:e007917. doi:10.1161/CIRCOUTCOMES.121.007917
46. Muñoz-Price LS, Nattinger AB, Rivera F, et al. Racial disparities in incidence and outcomes among patients with COVID-19. *JAMA Netw Open*. 2020;3:e2021892. doi:10.1001/jamanetworkopen.2020.21892
47. Crimmins EM. Social hallmarks of aging: suggestions for geroscience research. *Ageing Res Rev*. 2020;63:101136. doi:10.1016/j.arr.2020.101136
48. Avila-Rieger J, Turney IC, Vonk JMJ, et al. Socioeconomic status, biological aging, and memory in a diverse national sample of older US men and women. *Neurology*. 2022;99:e2114–e2124. doi:10.1212/WNL.0000000000201032
49. Ganguli M, Albanese E, Seshadri S, et al. Population neuroscience: dementia epidemiology serving precision medicine and population health. *Alzheimer Dis Assoc Disord*. 2018;32:1–9. doi:10.1097/WAD.0000000000000237
50. Khoury MJ, Engelgau M, Chambers DA, Mensah GA. Beyond public health genomics: can Big Data and predictive analytics deliver precision public health? *Public Health Genomics*. 2018;21:244–250. doi:10.1159/000501465
51. Kulkarni AS, Gubbi S, Barzilai N. Benefits of metformin in attenuating the hallmarks of aging. *Cell Metab*. 2020;32:15–30. doi:10.1016/j.cmet.2020.04.001
52. Duque G, Lipsitz LA, Ferrucci L, Addie S, Carrington-Lawrence S, Kohanski R. Geroscience for the next chapter of medicine. *J Gerontol A Biol Sci Med Sci*. 2023;78:791–792. doi:10.1093/gerona/glad083