

The association between Body Roundness Index and epigenetic aging: insights from the Health and Retirement Study

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Abstract

Background

The Body Roundness Index (BRI) has been proved to be associated with several metabolic and age-related disorders, with epigenetic pathways potentially underlying these connections. We analyzed data from the Health and Retirement Database to investigate whether higher BRI is linked to epigenetic aging

Methods

Using cross-sectional data from the Health and Retirement Study, we investigated the relationship between BRI and epigenetic aging. Epigenetic age acceleration (EAA) was calculated from five established DNA methylation clocks as the residual values from regressing epigenetic age on chronological age. The continuous associations were evaluated using linear regression and restricted cubic spline models. Subgroup analyses were conducted to assess consistency across different population strata. Logistic regression was applied to examine the link between BRI and accelerated aging ($EAA > 0$).

Results

A total of 1,801 participants aged ≥ 50 years were included in this cross-sectional analysis, with a mean BRI of 6.01. Linear regression analyses demonstrated that higher BRI was significantly associated with increased epigenetic age acceleration based on GrimAge, PhenoAge, and DunedinPoAm. These findings remained consistent in restricted cubic spline analyses and across subgroup analyses. Logistic regression models further supported these associations, showing that the odds of accelerated aging rose by 19.7% for GrimAge, 31.8% for PhenoAge, and 38.8% for DunedinPoAm for each 2.27-unit increase in BRI.

Conclusion

BRI was strongly associated with epigenetic age acceleration measured by GrimAge, PhenoAge, and DunedinPoAm, suggesting that increased visceral adiposity may contribute to epigenetic alterations.

Introduction

With the rapid progression of global population aging and the continuous increase in life expectancy, the assessment, prevention, and intervention of aging have attracted growing scientific and public health attention. Biological age has been proposed as a measure to evaluate an individual's physiological function and aging status. Compared with chronological age, biological age provides a more accurate reflection of the heterogeneity in physiological decline and functional capacity among individuals[1]. DNA methylation is a common epigenetic modification, and methylation levels at specific CpG sites have been shown to correlate with age[2]. By applying machine learning methods to methylation levels at specific CpG sites, various epigenetic clocks have been developed to estimate chronological age, biological age, physiological status, morbidity, and mortality risk[3]. Currently, epigenetic clocks are generally categorized into three generations[4]. First-generation epigenetic clocks, such as the Horvath and Hannum clocks, were primarily developed as age estimators to predict an individual's chronological age [5, 6]. Second-generation epigenetic clocks, such as PhenoAge and GrimAge, were developed to better reflect biological age and demonstrate improved predictive performance for health outcomes[7, 8]. Third-generation epigenetic clocks, such as DunedinPoAm, are designed to quantify the rate of biological aging [9]. People who are epigenetically older may have different health outcomes compared with those who are epigenetically younger[10]. The value of Epigenetic age acceleration (EAA) can be quantified either by calculating the difference between biological and chronological age or by regressing biological age on chronological age and using the resulting residuals as the measure of deviation[11–13].

Traditional measures such as body mass index (BMI) have been shown to be associated with epigenetic aging[14, 15]. However, BMI has limitations in assessing visceral adiposity tissue and fat distribution[16]. The Body Roundness Index (BRI) is a novel anthropometric measure that incorporates waist circumference and provides a better assessment of visceral adiposity tissue compared with traditional indicators[17]. Existing studies have shown that BRI is associated with various diseases and demonstrates unique advantages in predicting metabolic syndrome and cardiovascular events[18–20]. Using data from the NHANES database, previous research has demonstrated that BRI is significantly associated with epigenetic age acceleration of PhenoAge[21]. However, the associations between BRI and other epigenetic clocks, such as Horvath and GrimAge, remain largely unexplored. In this study, we used data from the Health and Retirement Study to investigate the relationship between BRI and epigenetic age acceleration across five established epigenetic clocks: Horvath, Hannum, GrimAge, PhenoAge, and DunedinPoAm.

Method

Data Sources and Study Population

This study used epigenetic clock data from the 2016 HRS Venous Blood Study (Nov, v1.0) and longitudinal data from the RAND HRS Longitudinal File 2022[22–24]. The Health and Retirement Study (HRS) is a longitudinal survey that includes a nationally representative sample of approximately 20,000 adults in the United States. The HRS (Health and Retirement Study) is sponsored by the National Institute on Aging (grant numbers NIA U01AG009740 and NIA R01AG073289) and is conducted by the University of Michigan. DNA methylation data were collected from a subsample of participants in the 2016 Venous Blood Study (N = 4,104), and these data which passed quality control were used to generate a dataset containing 13 epigenetic clocks (N = 4,018). After merging the Epigenetic Clocks dataset with longitudinal HRS data and applying data cleaning and exclusion, a final analytical sample of 1,801 participants was obtained. The detailed of data processing is illustrated in Fig. 1.

The calculation of BRI (Body Roundness Index)

Participants were asked to stand in an upright position with their arms elevated, and waist circumference (WC) was measured at the level of the umbilicus by trained interviewers. WC values were recorded in inches and rounded to the nearest quarter inch. Height was based on self-report. After converting WC into meters, the Body Roundness Index (BRI) was calculated using the established equation[17].

$$BRI = 364.2 - 365.5 \times \sqrt[2]{1 - \left(\frac{WC \div 2\pi}{0.5 \times height} \right)^2}$$

Epigenetic Clocks and Epigenetic Age Acceleration

The present study focused on five epigenetic aging biomarkers, including Horvath, Hannum, GrimAge, PhenoAge and DunedinPoAm. To quantify the value of epigenetic age acceleration (EAA), each clock was regressed on chronological age, and the resulting residuals were used as indices of epigenetic age acceleration. For DunedinPoAm, the age-adjusted residual was defined as *Age-adjusted DunedinPoAm*, whereas for the remaining clocks, acceleration measures were named by appending the suffix “Accel” to the original clock variable[25]. Based on whether EAA values were greater than zero, the epigenetic aging pattern of participants were classified into two groups: Accelerated aging (AA) and Decelerated aging (DA)[26, 27].

Covariates

In this study, we included several covariates that may act as potential confounders. These variables were mainly categorized into demographics, lifestyle factors, and disease status that may influence epigenetic clocks. The demographic variables included age, sex, marital status, education level, residence, and race. Lifestyle factors included alcohol consumption, smoking status, physical activity, and BMI. Regarding disease status, we mainly assessed whether participants had ever been diagnosed

with the following conditions: high blood pressure, diabetes, cancer, lung disease, heart problems, stroke, Psyche problems, or sleep disorders. Alcohol consumption was assessed based on three questionnaire items: (1): Ever drinks any alcohol; (2): days/week drinks; (3): drinks/day when drinks. By multiplying the responses to question (2) and question (3), we were able to estimate the weekly alcohol intake among participants who reported drinking. Based on this estimated weekly alcohol intake, participants were categorized into **Never drink**, **Low/moderate drinkers**, and **Heavy drinkers** following the criteria below: (1) **Never drink**: Participants who had never consumed alcohol or whose calculated weekly alcohol intake was zero; (2) **Low/moderate drinkers**: Male participants ≤ 14 drinks per week or female participants ≤ 7 drinks per week; (3) **Heavy drinkers**: Male participants > 14 drinks per week and female participants > 7 drinks per week[28]. A categorical variable for BMI was created based on the following criteria: (1) **Non-overweight**: BMI < 25 ; (2) **Overweight**: $25 \leq \text{BMI} < 30$; (3) **Obese**: $30 \leq \text{BMI}$. Based on the reported frequency of vigorous and moderate physical activities, participants meeting any of the following criteria were classified as **physically active**; otherwise, they were categorized as **physically inactive**: (a) Engaging in vigorous physical activity every day, more than once per week, or once per week. (b) Engaging in moderate physical activity every day or more than once per week[29].

Statistical Analysis

BRI was categorized into four groups (Q1–Q4) based on its 25th (4.539), 50th (5.642), and 75th (7.024) percentiles. Continuous variables were presented as median (interquartile range), whereas categorical variables were summarized as counts (percentages). Group differences were assessed using the Kruskal–Wallis rank-sum test for continuous variables and the Chi-square test for categorical variables. To investigate the association between BRI and EAA, multiple linear regression models were constructed, and residual Q-Q plots were used to evaluate model fit. Model 1 included sex, race, urbanicity, marital status, and education level. Model 2 further adjusted for drink, smoking status, physical activity, and BMI. Model 3 additionally included disease status. Variance inflation factors (VIFs) were calculated to assess multicollinearity, and all values were below 5. Restricted cubic spline (RCS) analysis with full adjustment was then applied to examine potential nonlinear relationships (knots = four: 5th, 35th, 65th, and 95th percentiles). To assess the consistency of associations across different subgroups, stratified analyses were conducted based on age, sex, education level, smoking status, physical activity, and disease conditions. Statistical interaction was considered significant when the interaction term had a P value < 0.05 . Finally, logistic regression was performed to evaluate the association between BRI and the risk of being accelerated aging.

Sensitivity analysis

First, participants with missing data on demographics, height, or waist circumference were excluded. The missing of remaining covariates was less than 10%, as shown in **Supplementary Fig. 1**, and multiple imputation was performed using the *mice* package (maxit = 50). Second, outliers in BRI were removed based on the criterion of mean ± 3 SD, and the distribution of BRI is presented in **Supplementary Fig. 2**. Both linear and logistic regression analyses were conducted to examine the association, adjusting for covariates across multiple models to evaluate the robustness of the findings. Subgroup analyses were also performed, and forest plots were generated to assess whether the associations remained consistent across subgroups and to determine the presence of potential interaction effects.

Results

Basic characteristics

After data cleaning, a total of 1,801 participants were included in the analysis, consisting of 1,039 females and 762 males. All participants were aged 50 years or older. The mean BRI was 6.01, with a standard deviation of 2.27, and the maximum observed value was 18.34. Among the participants, 779 showed accelerated aging on GrimAge, 855 on PhenoAge, 954 on Horvath clock, 879 on Hannum clock, and 818 on DunedinPoA. Table 1 presents the baseline characteristics stratified by BRI quartiles. A clear trend was observed in Fig. 2: the proportion of individuals with accelerated aging increased across the four BRI groups for most epigenetic clocks especially for Horvath, PhenoAge, GrimAge. Regarding demographics and lifestyle characteristics, significant differences were found across BRI categories for all variables except marital status ($P = 0.122$) and alcohol consumption ($P =$

0.176). For disease conditions, most diseases condition showed increasing prevalence with higher BRI levels. However, cancer prevalence did not differ significantly among the four groups ($P = 0.516$).

Table 1
Baseline characteristics of participants according to quartiles of the Body Roundness Index.

		Q1	Q2	Q3	Q4	P
		N = 452	N = 457	N = 442	N = 450	
Age		69.00 [61.00, 77.00]	68.00 [61.00, 77.00]	69.00 [62.00, 79.00]	66.00 [60.00, 76.00]	0.003
Gender						
	Male	192 (42.48)	216 (47.26)	204 (46.15)	150 (33.33)	< 0.001
	Female	260 (57.52)	241 (52.74)	238 (53.85)	300 (66.67)	
Marital status						
	Married/partnered	280 (61.95)	300 (65.65)	283 (64.03)	258 (57.33)	0.122
	Separated/Divorced	71 (15.71)	63 (13.79)	59 (13.35)	75 (16.67)	
	Widowed	72 (15.93)	79 (17.29)	82 (18.55)	88 (19.56)	
	Never married	29 (6.42)	15 (3.28)	18 (4.07)	29 (6.44)	
Urbanicity						
	Urban	239 (52.88)	262 (57.33)	244 (55.20)	213 (47.33)	0.049
	Suburban	96 (21.24)	92 (20.13)	104 (23.53)	110 (24.44)	
	EX-urban	117 (25.88)	103 (22.54)	94 (21.27)	127 (28.22)	
Race						
	White/Caucasian	356 (78.76)	363 (79.43)	328 (74.21)	312 (69.33)	0.004
	Black/African American	67 (14.82)	60 (13.13)	74 (16.74)	101 (22.44)	
	Other	29 (6.42)	34 (7.44)	40 (9.05)	37 (8.22)	
Education						
	Less than high school	56 (12.39)	80 (17.51)	82 (18.55)	83 (18.44)	0.007
	GED or high school	138 (30.53)	157 (34.35)	140 (31.67)	166 (36.89)	
	College or above	258 (57.08)	220 (48.14)	220 (49.77)	201 (44.67)	
Smoke						
	Never smoke	199 (44.52)	196 (42.98)	201 (45.89)	193 (42.98)	0.033
	Former smoker	178 (39.82)	207 (45.39)	200 (45.66)	208 (46.33)	
	Current smoker	70 (15.66)	53 (11.62)	37 (8.45)	48 (10.69)	
Drink						
	Never drink	177 (39.25)	205 (45.05)	180 (41.00)	214 (47.87)	0.176
	Low/Moderate drinker	241 (53.44)	222 (48.79)	233 (53.08)	208 (46.53)	
	Heavy drinker	33 (7.32)	28 (6.15)	26 (5.92)	25 (5.59)	
Physical activity						

		Q1	Q2	Q3	Q4	P
		N = 452	N = 457	N = 442	N = 450	
	Physically inactive	130 (28.76)	177 (38.82)	191 (43.21)	251 (55.78)	< 0.001
	Physically active	322 (71.24)	279 (61.18)	251 (56.79)	199 (44.22)	
BMI category						
	Non-overweight	335 (74.78)	114 (25.05)	25 (5.68)	3 (0.68)	< 0.001
	Overweight	109 (24.33)	299 (65.71)	206 (46.82)	36 (8.13)	
	Obese	4 (0.89)	42 (9.23)	209 (47.50)	404 (91.20)	
BMI		23.30 [21.60, 25.00]	26.60 [24.95, 28.30]	29.70 [27.58, 31.90]	35.50 [32.60, 39.50]	< 0.001
High blood pressure						
	No	239 (52.88)	190 (41.58)	136 (30.77)	88 (19.56)	< 0.001
	Yes	213 (47.12)	267 (58.42)	306 (69.23)	362 (80.44)	
Diabetes						
	No	392 (86.73)	349 (76.37)	290 (65.61)	246 (54.67)	< 0.001
	Yes	60 (13.27)	108 (23.63)	152 (34.39)	204 (45.33)	
Cancer						
	No	385 (85.18)	378 (82.71)	365 (82.58)	384 (85.33)	0.516
	Yes	67 (14.82)	79 (17.29)	77 (17.42)	66 (14.67)	
Lung disease						
	No	420 (92.92)	410 (89.72)	396 (89.59)	382 (84.89)	0.001
	Yes	32 (7.08)	47 (10.28)	46 (10.41)	68 (15.11)	
Heart problem						
	No	364 (80.53)	347 (75.93)	320 (72.40)	308 (68.44)	< 0.001
	Yes	88 (19.47)	110 (24.07)	122 (27.60)	142 (31.56)	
Stroke						
	No	424 (93.81)	413 (90.37)	403 (91.18)	397 (88.22)	0.034
	Yes	28 (6.19)	44 (9.63)	39 (8.82)	53 (11.78)	
Psyche problem						
	No	374 (82.74)	382 (83.59)	354 (80.09)	329 (73.11)	< 0.001
	Yes	78 (17.26)	75 (16.41)	88 (19.91)	121 (26.89)	
Sleep disorder						

	Q1	Q2	Q3	Q4	P
	N = 452	N = 457	N = 442	N = 450	
No	414 (91.59)	402 (87.96)	364 (82.35)	300 (66.67)	< 0.001
Yes	38 (8.41)	55 (12.04)	78 (17.65)	150 (33.33)	
HorvathAccel	-0.37 [-3.74, 2.98]	0.26 [-2.75, 4.19]	0.72 [-3.10, 4.08]	0.76 [-2.70, 3.93]	0.023
HannumAccel	-0.91 [-4.05, 1.97]	0.15 [-3.63, 3.43]	-0.15 [-3.60, 3.27]	0.30 [-2.57, 3.62]	< 0.001
GrimAgeAccel	-1.41 [-4.51, 3.43]	-1.08 [-3.55, 2.81]	-0.76 [-2.86, 2.50]	-0.12 [-2.40, 3.20]	0.001
PhenoAgeAccel	-1.68 [-5.85, 3.18]	-0.57 [-4.97, 3.80]	-0.50 [-4.54, 4.17]	1.13 [-2.76, 4.48]	< 0.001
Age-adjusted MPOA	-0.02 [-0.08, 0.05]	-0.02 [-0.08, 0.04]	-0.01 [-0.06, 0.05]	0.01 [-0.04, 0.07]	< 0.001

Association between BRI and Epigenetic age acceleration

Table 2 presents the linear regression results examining the association between BRI and each epigenetic clock. Multiple models were constructed with progressive covariate adjustment, and model fit for the fully adjusted Model 3 was evaluated using residual Q–Q plots (**Supplementary Fig. 3**). In the fully adjusted model, BRI was positively associated with Age-adjusted DunedinPoAm ($\beta = 0.006$, $P < 0.001$), PhenoAgeAccel ($\beta = 0.351$, $P < 0.001$), GrimAgeAccel ($\beta = 0.178$, $P = 0.002$), and HannumAccel ($\beta = 0.188$, $P = 0.022$). However, the association between BRI and HorvathAccel was not statistically significant ($\beta = 0.141$, $P = 0.159$). Restricted cubic spline analysis was then performed (Fig. 3). The results indicated an overall significant association between BRI and GrimAgeAccel (P for overall = 0.013; P for nonlinear = 0.696), Age-adjusted DunedinPoAm (P for overall < 0.001; P for nonlinear = 0.573), and PhenoAgeAccel (P for overall = 0.008; P for nonlinear = 0.609), with no evidence of nonlinearity. Subgroup analyses were subsequently conducted for GrimAgeAccel, Age-adjusted DunedinPoAm, and PhenoAgeAccel to assess the stability of associations across different strata. As shown in Fig. 4, the associations between BRI and these clocks remained largely consistent across most subgroups. Interaction analyses further suggested potential effect modification: For GrimAgeAccel, interactions were observed with hypertension (P for interaction = 0.007) and heart disease (P for interaction = 0.033). For PhenoAgeAccel, interactions were detected with sex (P for interaction = 0.041) and smoking status (P for interaction = 0.029). For Age-adjusted DunedinPoAm, interactions were identified with education level (P for interaction = 0.039) and hypertension (P for interaction = 0.022).

Table 2
Associations between BRI and epigenetic aging indicators based on multivariable linear regression models.

		Age-adjusted DunedinPoAm	PhenoAgeAccel	GrimAgeAccel	HannumAccel	HorvathAccel
Crude model	β	0.004	0.401	0.143	0.203	0.141
	SE	0.001	0.070	0.049	0.056	0.065
	<i>P</i>	< 0.001***	< 0.001***	0.004**	< 0.001***	0.031*
Model 1	β	0.004	0.401	0.162	0.259	0.165
	SE	0.001	0.071	0.045	0.055	0.066
	<i>P</i>	< 0.001***	< 0.001***	< 0.001***	< 0.001***	0.012*
Model 2	β	0.007	0.449	0.263	0.219	0.142
	SE	0.001	0.104	0.056	0.081	0.098
	<i>P</i>	< 0.001***	< 0.001***	< 0.001***	0.007**	0.146
Model 3	β	0.006	0.351	0.178	0.188	0.141
	SE	0.001	0.106	0.056	0.082	0.100
	<i>P</i>	< 0.001***	< 0.001***	0.002**	0.022*	0.159
Notes: Values represent regression coefficients (β), standard errors (SE), and <i>P</i> values.						

Model 1 adjusted for Gender, Education, Urbanicity, Marital status, Race.

Model 2 further adjusted for Smoking status, Drink, BMI and Physical activity.

Model 3 additionally adjusted for disease conditions.

P* < 0.05; *P* < 0.01; ****P* < 0.001.

Association between BRI and Epigenetic aging pattern

Table 3 presents the results of the multivariable logistic regression analyses. For each epigenetic clock, logistic regression models were constructed with same adjustment, including the crude model, Model 1, Model 2, and the fully adjusted Model 3. After full adjustment, BRI was significantly associated with accelerated aging defined by GrimAge, PhenoAge, and DunedinPoAm (PhenoAge: OR = 1.129, *P* < 0.001; GrimAge: OR = 1.082, *P* = 0.046; DunedinPoAm: OR = 1.155, *P* < 0.001). When BRI was categorized by quartiles, a similar trend was observed. Compared with the lowest quartile (Q1), only Q3 showed a statistically significant association for PhenoAge (*P*_{Q3} = 0.003) and DunedinPoAm (*P*_{Q3} = 0.039). For GrimAge, both Q2 and Q3 were significantly associated with accelerated aging compared with Q1 (*P*_{Q2} = 0.041; *P*_{Q3} = 0.033). After standardization, each 1-SD increase in BRI (SD = 2.27) was associated with an increased risk of accelerated aging of 31.8% for PhenoAge (*P* < 0.001), 19.7% for GrimAge (*P* = 0.046), and 38.8% for DunedinPoAm (*P* < 0.001). A significant dose–response pattern was observed for all three clocks (*P* for trend: 0.005, 0.038, and 0.033, respectively).

Table 3
Multivariable logistic model for aging status of GrimAge, PhenoAge, DunedinPoAm.

		Cruel Model		Model 1		Model 2		Model 3	
		OR	P value	OR	P value	OR	P value	OR	P value
PhenoAge	BRI	1.139	< 0.001***	1.141	< 0.001***	1.158	< 0.001***	1.129	< 0.001***
	Quartiles of BRI								
	Q1	Ref		Ref		Ref		Ref	
	Q2	1.241	0.109	1.217	0.150	1.335	0.067	1.239	0.180
	Q3	1.406	0.012*	1.358	0.026*	1.540	0.019*	1.337	0.122
	Q4	2.145	< 0.001***	2.167	< 0.001***	2.383	< 0.001***	1.948	0.003**
	Per 1 SD increase	1.344	< 0.001***	1.349	< 0.001***	1.397	< 0.001***	1.318	< 0.001***
	P for trend	< 0.001***		< 0.001***		< 0.001***		0.005**	
GrimAge	BRI	1.058	0.007**	1.077	0.001**	1.132	0.001**	1.082	0.046*
	Quartiles of BRI								
	Q1	Ref		Ref		Ref		Ref	
	Q2	1.157	0.280	1.069	0.653	1.603	0.016*	1.419	0.082
	Q3	1.216	0.151	1.121	0.439	2.028	0.001**	1.609	0.041*
	Q4	1.501	0.003**	1.572	0.002**	2.611	< 0.001***	1.819	0.033*
	Per 1 SD increase	1.136	0.007**	1.183	0.001**	1.325	0.001**	1.197	0.046*
	P for trend	0.003**		0.002**		< 0.001***		0.038*	
DunedinPoAM	BRI	1.096	< 0.001***	1.099	< 0.001***	1.175	< 0.001***	1.155	< 0.001***
	Quartiles of BRI								
	Q1	Ref		Ref		Ref		Ref	
	Q2	0.946	0.682	0.898	0.438	1.046	0.793	0.962	0.825
	Q3	1.059	0.669	0.992	0.955	1.354	0.128	1.175	0.430
	Q4	1.547	0.001**	1.505	0.003**	2.020	0.003**	1.668	0.039*
	Per 1 SD increase	1.232	< 0.001***	1.239	< 0.001***	1.442	< 0.001***	1.388	< 0.001***
	P for trend	< 0.001***		0.002**		0.003**		0.033*	

Discussion

In this study, we examined the association between BRI and epigenetic aging using five established epigenetic clocks. To our knowledge, this is the first study to comprehensively assess this relationship across multiple generations of epigenetic clocks. Our findings demonstrated significant linear associations between BRI and Age-adjusted DunedinPoAm, PhenoAgeAccel, and GrimAgeAccel. The restricted cubic spline analysis further supported these results, indicating statistically significant overall associations without evidence of nonlinear patterns. Moreover, as BRI increased, the regression coefficient (β) also increased, indicating that the effect of BRI on EAA was stronger at higher levels of BRI. In addition, subgroup analyses showed that these associations remained largely consistent across most population strata. Logistic regression analysis revealed that each one-unit increase in BRI was associated with an increased risk of accelerated aging by 8.2% for GrimAge, 12.9% for PhenoAge, and 15.5% for DunedinPoAm. Finally, no statistically significant associations were observed between BRI and epigenetic age acceleration defined by the first-generation clocks (Horvath and Hannum).

The Hannum clock is a DNA methylation–based age estimator developed using adult blood samples, and its model was trained using a selected set of 71 CpG sites[6]. Although it is a single-tissue DNA methylation age estimator, studies have shown that it, along with PhenoAge, predicts life expectancy more accurately than many other blood-based biomarkers[3]. Horvath's clock is the first pan-tissue epigenetic age estimator, developed using data from 51 healthy tissues and cell types. It is based on 353 CpG sites and was trained and validated using over 8,000 publicly available microarray samples. To date, it remains one of the most accurate estimators of chronological age[5]. However, although first-generation epigenetic clocks perform well in estimating chronological age, they show limited ability in predicting morbidity and mortality. To address this limitation, Levine et al. developed a second-generation aging clock, PhenoAge, based on 513 CpG sites and incorporating clinical biomarkers strongly associated with disease incidence and mortality. This model has been demonstrated to provide improved predictive power for all-cause mortality, cancer, and functional decline[8]. GrimAge was developed using DNA methylation–derived estimates of seven plasma protein biomarkers along with a methylation-based surrogate for smoking pack-years. It has demonstrated strong predictive ability for time-to-death, incident coronary heart disease, and cancer. In addition, GrimAge has been reported to be associated with nonalcoholic fatty liver disease and excessive visceral adiposity[7]. Unlike the first-generation epigenetic clocks, GrimAge and PhenoAge were developed based on clinical phenotypic age measures. These clocks demonstrate substantially stronger associations with aging-related diseases and mortality compared with earlier DNA methylation–based biomarkers [30]. DunedinPoAm is a DNA methylation–based biomarker developed to capture the pace of biological aging rather than chronological age. It enables the assessment of an individual's rate of biological aging at a single time point. Evidence suggests that people with accelerated DunedinPoAm are susceptible to poorer physical and cognitive function, as well as greater subjective signs of aging[9].

BRI is a novel anthropometric index based on an elliptical body model. Compared with traditional measures such as BMI, it provides a more accurate assessment of individual body fat percentage and visceral adipose tissue volume[17]. Zhang et al., using data from the NHANES database, reported a U-shaped association between BRI and all-cause mortality among U.S. adults[31]. Hu et al., using the Klemm–Doubal method for biological age (KDM-BA), found that accelerated biological aging partially mediated the relationship between obesity and the incidence of cardiovascular disease[32]. Similarly, Zhu et al. found that accelerated biological aging partially mediated the association between BRI and cardiometabolic multimorbidity[33]. Dong et al. found that both BRI and serum estradiol were associated with accelerated PhenoAge in men, and their coexistence may further strengthen this association[34]. Regarding the relationship between BRI and cancer, Luo et al. reported a nonlinear association, finding that when BRI exceeded 5.06, the incidence of cancer increased by approximately 10%[35]. Additionally, Wang et al. also found a nonlinear positive association between higher BRI and accelerated biological aging[36]. Moreover, this association may be influenced by female sex and intake of ascorbic acid. Obesity can induce changes in the local inflammatory and regulatory cells within visceral adipose tissue (VAT)[37]. Furthermore, studies have shown that obesity can lead to redox imbalance in the body. Excess reactive oxygen species (ROS) in adipose tissue can cause excessive cellular damage, mitochondrial dysfunction, chronic inflammation, and dysregulated autophagy and apoptosis, ultimately contributing to aging at multiple levels[38].

Our study confirmed the association between BRI and second-generation clocks (GrimAge and PhenoAge) as well as the third-generation clock (DunedinPoAm). The results suggest that obesity, particularly abdominal obesity, is closely related to accelerated aging. Higher BRI could increase the risk of all-cause mortality and age-related diseases, and this process might

have be mediated by epigenetic aging. Tan et al. proposed that obesity can be considered a disease of accelerated aging[38], This perspective are consistent with our results. In addition to assessing aging, epigenetic clocks provide a means to evaluate the effectiveness of aging interventions. Fitzgerald et al. reported that dietary and lifestyle interventions can reduce an individual's Horvath clock age[39]. Lu et al. found that changes in DNA methylation patterns are involved in the processes of aging and functional rejuvenation[40]. Ammous et al. demonstrated that physical exercise can effectively slow down epigenetic aging[29], Therefore, we reasonably speculate that physical exercise, dietary control, and reduction of visceral fat may have complex relationships in slowing epigenetic aging, although further studies are needed to explore this hypothesis.

Our study has several limitations. First, as a cross-sectional study, it is subject to potential reverse causation. Second, when calculating BRI, height data were self-reported, and waist circumference measurements did not account for clothing, which could potentially introduce bias. Lastly, This study was conducted at a single center, which may limit the generalizability of the findings. Further longitudinal and multicenter studies are needed to confirm the relationship between BRI and epigenetic aging.

Conclusion

Our findings indicate that higher BRI is strongly associated with accelerated epigenetic aging as measured by GrimAge, PhenoAge, and DunedinPoAm. Moreover, the magnitude of this association increased across higher BRI levels, suggesting that greater visceral adiposity may play a key role in promoting epigenetic aging. Furthermore, epigenetic alterations may contribute to the development of various diseases in individuals with high BRI and are associated with increased all-cause mortality.

Declarations

Ethical Approval

This study was conducted using publicly available data, so it was exempt from Institutional Review Board (IRB) approval.

Author contribution declaration

All authors on the list have made substantial contributions to this research, and are accountable for all aspects of the work. Specifically, Sihan Chen led the main part of data analysis and drafted most of the original manuscript; Bo Chen prepared figures and tables for the manuscript and reviewed the original manuscript; Biao Ran, Shibo Jian, Jie Chen, Jingxing Bai, Yin Huang, Zeyu Chen provide suggestions and improved data analysis; Qiang Wei, Qiang Dong, Dehong Cao, Liangren Liu reviewed this research and supervised the research process.

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Conflict of Interest

The authors declare that this study have no commercial and financial relationships which could results in any potential conflict of interest.

Availability of data and materials

The data of this article comes from Health and retirement study and Rand HRS product, and the part of coding will be available for those who send email to correspondence. This study was conducted using publicly available data from Health and Retirement study (HRS). The HRS is sponsored by the National Institute on Aging (grant numbers NIA U01AG009740 and NIA R01AG073289) and is conducted by the University of Michigan. Links of datasets used in this article: **HRS Epigenetic clocks:** <https://doi.org/10.7826/LPIK1762>; **2016 RAND HRS Fat File:** 2016 RAND HRS Fat File | Health and Retirement Study.

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Figures

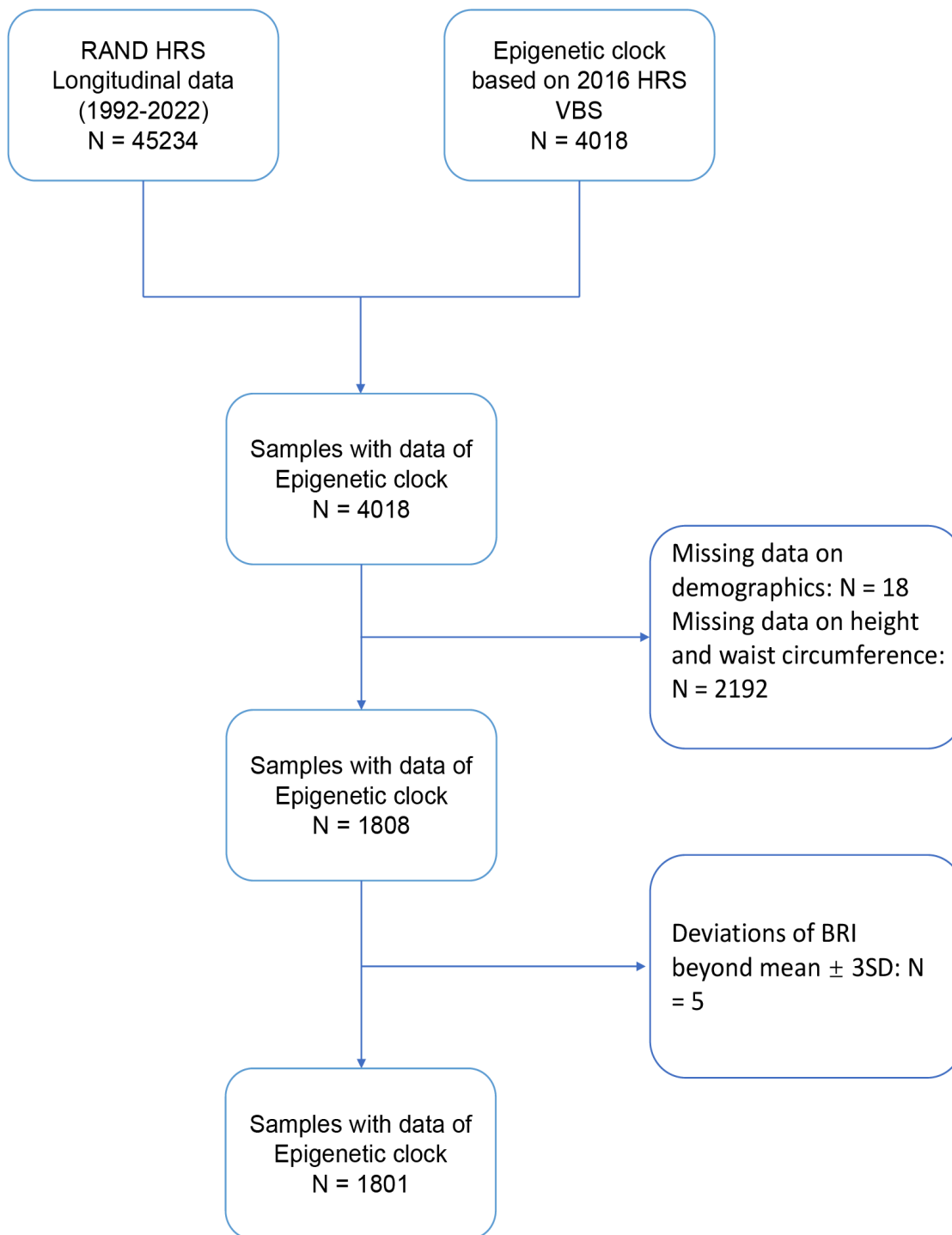


Figure 1

Flowchart of data processing

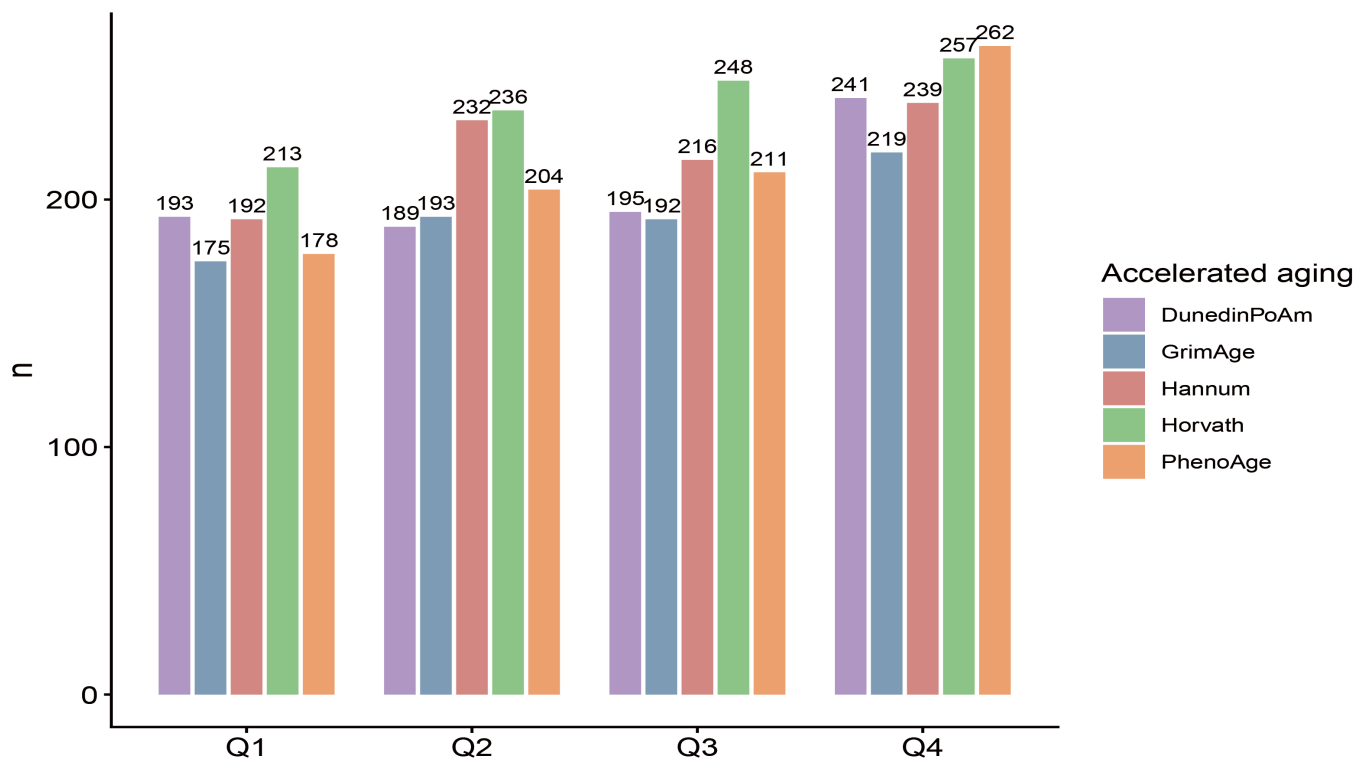


Figure 2

the number of participants with accelerated aging in different epigenetic clocks across BRL groups

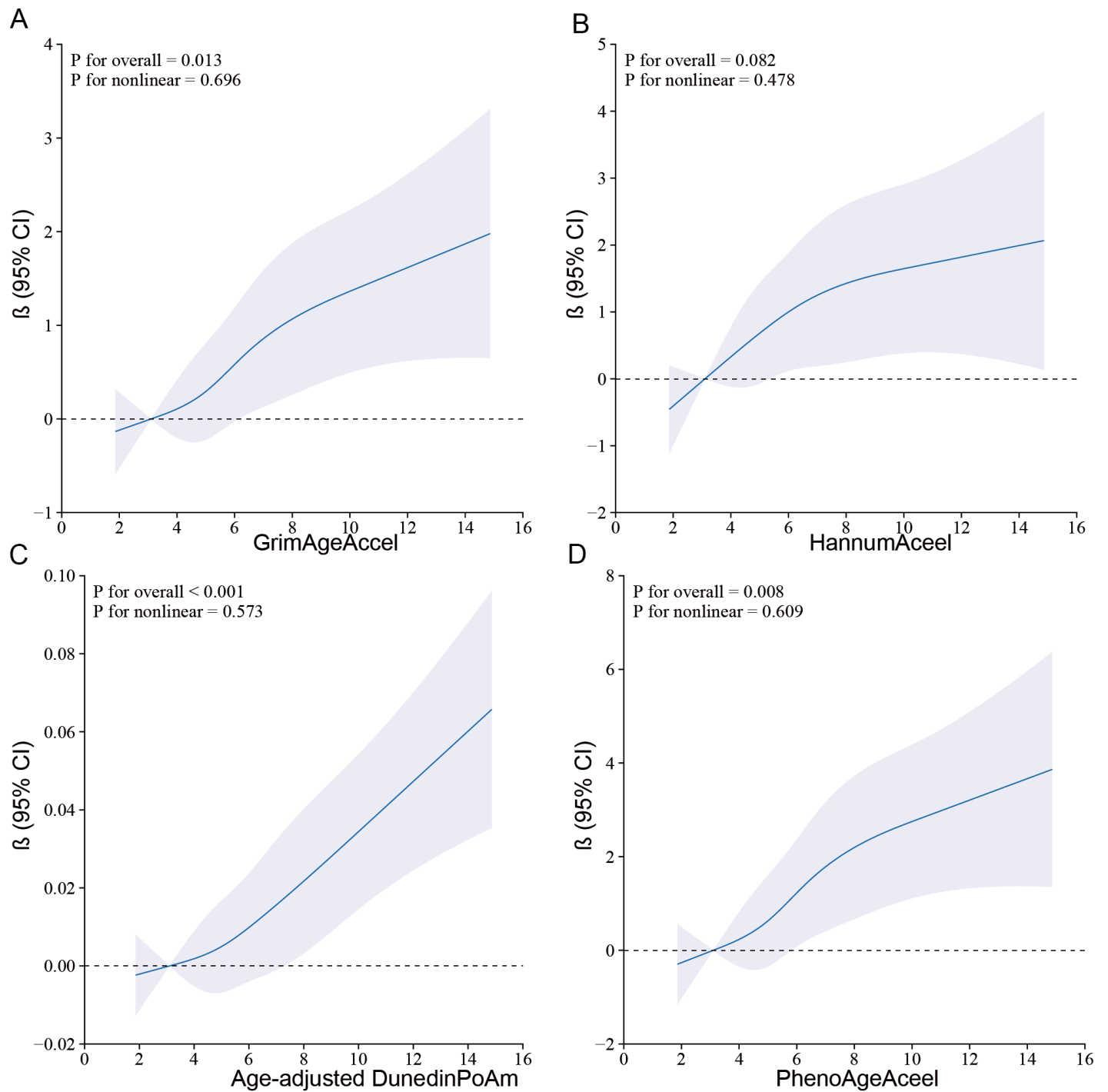


Figure 3

Fully adjusted RCS for GrimAgeAccel, HannumAccel, Age-adjusted DunedinPoAm, PhenoAgeAccel. (A) RCS for GrimAgeAccel; (B) RCS for HannumAccel; (C) RCS for Age-adjusted DunedinPoAm; (D) RCS for PhenoAgeAccel

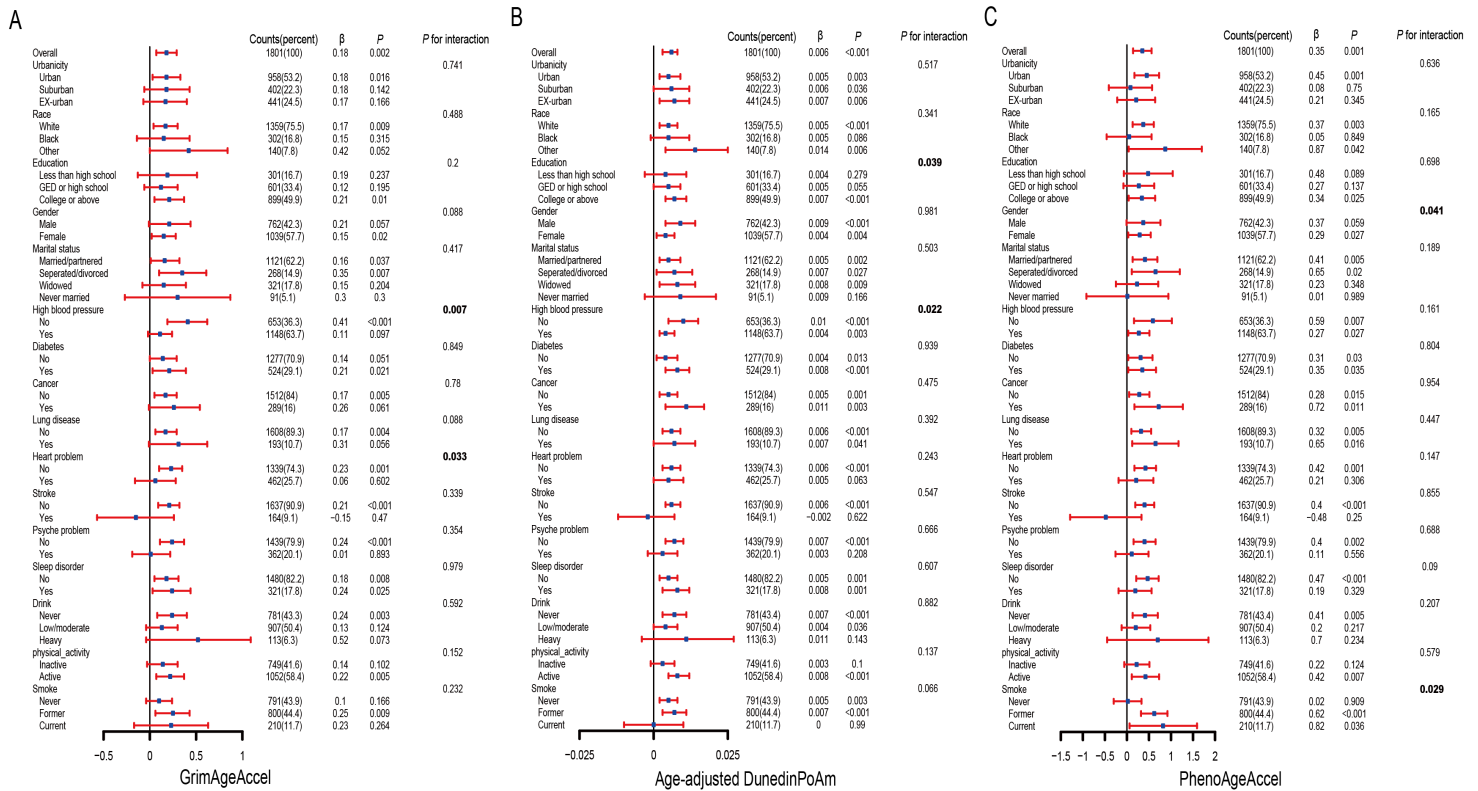


Figure 4

Subgroup analyses for GrimAgeAccel(A), PhenoAgeAccel(B), and age-adjusted DunedinPoAm(C).

Supplementary Files

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