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Racial and sex differences in biological and chronological heart age in the Coronary Artery Risk Development in Young Adults study

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ABSTRACT

Purpose: Calculation of a biological heart age offers an alternative to absolute risk for characterizing cardiovascular risk by describing risk relative to an individual with normal health. We examined risk factors contributing to differences between biological and chronological heart age in young adults.
Methods: The Coronary Artery Risk Development in Young Adults study included 2264 Black and White men and women who attended examination years 10 through 25. We estimated biological heart age using the nonlaboratory-based Framingham 10-year cardiovascular disease risk calculator. Trends in risk factors were examined cross-sectionally and longitudinally.
Results: Biological heart ages for Black participants were 5.6 years older than their chronological ages over 15 years ($P < .001$). In longitudinal analyses, urinary albumin–creatinine ratio and alcohol intake were statistically significantly related to higher biological compared with chronological heart age, whereas physical activity and education were statistically significantly related to negative heart age differences ($P < .001$). Trends were similar in cross-sectional analyses at all time points.
Conclusions: Most risk factors driving biological heart age, including race, education, physical activity, and urinary albumin–creatinine ratio, contributed to heart age differences cross-sectionally and longitudinally suggesting that risk factors related to adverse biological aging are important at younger and older ages.

Introduction

Biological heart age represents the functional age of the cardiovascular system of a person based on his or her cardiovascular risk factor profile [1,2]. Therefore, biological age offers another method for describing cardiovascular risk in individuals or groups beyond chronological age or probability of cardiovascular disease (CVD) event over time [2]. When compared with chronological age, biological age can quantify both the excess or favorable risk in an individual and be used to identify lifestyle factors that may contribute to these differences.

Biological heart age is not a new concept but thus far has not been widely used. The nonlaboratory-based Framingham 10-year CVD risk calculator was designed to provide an individual risk of experiencing a CVD event [1]. An analysis of data from the Behavioral Risk Factor Surveillance System (BRFSS) assessed biological heart age based on this risk score [1,2]. The authors of the BRFSS article found that biological heart age was significantly higher than chronological heart age for many adults in the United States. They observed the greatest differences between biological and chronological age in men, Blacks, and those with lower socioeconomic status, as indicated by education and household income [2]. This analysis was limited by the lack of longitudinal data and the need to estimate systolic blood pressure (SBP), which is not captured by the survey [2].

The Coronary Artery Risk Development in Young Adults (CARDIA) study offers an opportunity to reexamine the association between chronological and biological heart age over time with an emphasis on important demographic subgroups, specifically age,

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race, sex, and education. These subgroups were the recruitment strata for the cohort; therefore, the study has adequate distributions of these attributes [3]. In addition, the relatively young age of CARDIA participants in earlier examinations may identify risk factors or trends that are not apparent at older ages when competing comorbidities or medication use may obscure trends.

CARDIA is able to provide directly measured data for biological heart age calculations both cross-sectionally and longitudinally. Using data from CARDIA, we calculated biological heart age in study participants at each examination starting at age 30 years. We examined differences in biological and chronological heart age and determined which subgroups had the largest differences between biological and chronological age across examination years. We also assessed if established cardiovascular risk factors not included in the Framingham risk calculator were also associated with biological heart age.

Methods

Study design

The CARDIA study is a prospective cohort that enrolled 5115 participants between the ages of 18 and 30 years from 1985 to 1986. Enrollment was balanced across race, sex, age, and education. Participants were from Birmingham, AL; Chicago, IL; Oakland, CA; and Minneapolis, MN. Informed consent was obtained from all participants. The study design has been previously described in detail [3].

Biological heart age was calculated at four consecutive examinations to assess trends in risk factors. At examination years 10, 15, 20, and 25, there was high participant retention with 79%, 74%, 72%, and 72% of surviving participants returning for follow-up examinations, respectively. Of these participants, 3790, 3566, 3453, and 3406 individuals had sufficient data to calculate biological heart age at the four examination years, respectively. A total of 2489 individuals had complete data at all four examinations. Individuals who were aged less than 30 years at examination year 10 were excluded from analysis because their chronological age did not fall within the parameters of the calculator. In addition, pregnant women were excluded due to the potential impact on risk factors. One participant withdrew from the study. The final analyses included 2264 participants. Using data from these four examinations captured changes in biological heart age during early middle age.

Biological heart age

Biological heart age was derived from the nonlaboratory-based Framingham 10-year cardiovascular risk score, which was chosen for its relevance in and out of clinical settings. The Framingham risk score was developed for adults aged between 30 and 74 years based on sex, SBP, height, weight, smoking status, antihypertensive medication use, and diabetes status [1,2]. Using the Framingham risk score, biological heart age represents the age at which someone would have the same 10-year cardiovascular as someone of the same sex with normal health characteristics. Using this method, normal health was defined as a nonsmoker with an SBP of 125 mm Hg, body mass index (BMI) of 22.5 kg/m^2, and who does not have diabetes or use antihypertensive medication [1] (The CVD risk calculator may be accessed here: https://www.framinghamheartstudy.org/fhs-risk-functions/cardiovascular-disease-10-year-risk/)

Heart age difference was defined as biological heart age minus chronological heart age. A biological heart age less than the chronological age therefore resulted in a negative heart age difference that was indicative of someone with lower than expected risk for their age. Conversely, a biological heart age greater than the chronological heart age, which resulted in a positive heart age difference, indicated greater cardiovascular risk.

Thus, a hypothetical 40-year-old woman, with an SBP of 125 mm Hg and BMI of 22.5 kg/m^2 who did not smoke, have diabetes, or require treatment for hypertension would have a biological heart age of 40. Her biological and chronological ages would be the same, and her heart age difference would be 0. If her SBP were 110 mm Hg instead of 125 mm Hg, but the rest of her risk factors remained normal, then her biological heart age would be 35, and her heart age difference would be −5. If instead she was taking medication for hypertension, but all other characteristics remained normal, then her biological heart age would be 45, and her heart age difference would be 5.

Variable

Components of biological heart age were assessed throughout follow-up. Sex was self-reported. Participant age at each examination was calculated using date of birth, which was assessed by self-report. Smoking status and the use of antihypertensive medications were ascertained by self-report at each examination. Serum glucose concentrations were measured using the hexokinase method at Linco Research (St Charles, MO) through examination year 20 after which they were conducted at the Collaborative Studies Clinical Laboratory, University of Minnesota. Hemoglobin A1c was determined at the University of Minnesota (Minneapolis, MN) using the Tosoh G7 high-performance liquid chromatography instrument at examination years 25 and 30. Diabetes status was based on fasting glucose (≥126 mg/dL), 2-hour oral glucose tolerance test (≥ 200 mg/dL), hemoglobin A1c (≥6.5%), or the use of medication for diabetes when available. Study staff measured height, weight, and SBP using standard protocols [3].

Additional CVD risk factors of interest were also assessed throughout the CARDIA study. Race was assessed by self-report at baseline and confirmed at examination year 2. Alcohol consumption, education, and marital status were obtained by self-report at all examinations. Education was recorded as highest grade completed. Marital status was categorized as married or cohabiting, single, or separated, divorced, or widowed. Physical activity was characterized using a modified Baecke questionnaire [3]. Plasma total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were measured using enzymatic methods; high-density lipoprotein cholesterol levels were measured after dextran-sulfate-magnesium precipitation of other lipoproteins. Low-density lipoprotein cholesterol levels were estimated with the Friedewald equation for individuals with fasting triglyceride values less than 400 mg/dL [3–6]. Urinary albumin–creatinine ratio (UACR) was measured at examination years 10 through 25 with similar methods using a nephelometry-based assay by Dade Behring using a BN-II instrument. Detailed information on CARDIA study protocols have been described previously [3].

Statistical analysis

Heart age difference was the outcome of interest. Continuous demographic and health characteristics were assessed using univariate analyses to examine normality and determine if transformation was required. Data were presented as means and SDs for continuous variables and counts and percentages for categorical variables.

Linear regression was used to assess the associations between heart age difference and individual risk factors. For each of the four examination years analyzed, multiple linear regression models were used to assess risk factors cross-sectionally. Repeated measures linear regression models with a Toeplitz correlation structure

were used to examine longitudinal trends in the difference between biological and chronological age.

Variables included in the heart age derivation, specifically sex, SBP, height, weight, smoking status, antihypertensive medication use, and diabetes status, were not included in the models to avoid overadjustment. Both cross-sectional and longitudinal linear regression models were conducted in three stages. First, crude models were run, then the models were adjusted for race, study center, total cholesterol, and UACR, and finally for alcohol intake, physical activity, education, and marital status. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC), and statistical significance assessed as two-tailed type I errors of 0.05.

Results

Descriptive characteristics of CARDIA participants included and excluded from these analyses are in Table 1. Compared with the CARDIA participants who were not included in the analysis, the analytic sample had fewer Black participants ($P < .001$, data not shown). The participants in the analytic sample also were less likely to be treated for hypertension and had lower mean SBP at examination year 0 compared with those not included in analysis ($P < .001$ and .0155 respectively, data not shown). Participants included in the analysis were more likely to be married and had more years of education on average compared with CARDIA participants not included in the analysis ($P < .001$, data not shown). Prevalence of diabetes, mean alcohol intake, and mean BMI were lower in participants analyzed, but these differences were not statistically significant ($P = .7738$, .0667, and .3028 respectively, data not shown).

Cross-sectional trends are presented in Table 2. At examination year 10, on average, participants had lower biological ages than chronological ages, largely driven by low SBP and the low prevalence of diabetes and hypertension medication use. By examination year 15, biological age was greater than chronological age, and this trend continued through examination years 20 and 25.

Mean SBP, BMI, and total cholesterol increased across the examinations. The means for SBP remained below 120 mm Hg, BMI remained below 30 kg/m^2, and total cholesterol remained below 200 mg/dL. Prevalence of diabetes and antihypertensive medication use were higher at examination year 25 compared with examination year 10. At examination year 10, prevalence of diabetes and antihypertensive medication use were 2.1% and 2.6%, respectively. At examination year 25, 11.9% and 27.1% of participants reported diabetes and antihypertensive medication use, respectively. Fewer participants reported being current smokers at examination year 25 (14.4%) than examination year 10 (21.5%).

Cross-sectional associations between heart age difference and many risk factors were largely consistent among the examinations (Table 3). Total cholesterol and UACR were positively associated with heart age difference. Total cholesterol was statistically significantly associated with heart age difference at examination years 15, 20, and 25 (all $P < .0001$). UACR was statistically significantly associated with heart age difference at examination years 15, 20, and 25 (all $P < .0001$).

Race was associated with significant excess heart age after adjusting for all other variables and at all examinations. At examination year 10, biological heart age exceeded chronological age for Black participants by 2.6 years on average compared with Whites ($P < .001$). By examination year 25, this difference was 4.7 years ($P < .001$). Higher physical activity and education were associated with lower biological heart age compared with chronological age. Education was highly statistically significant at all four examinations (all $P < .0001$) with each additional year of education associated with between 0.5 and 0.8 lower biological heart ages on average. Physical activity was not statistically significant at examination year 10 but was significant at all subsequent examinations ($P = .0043$, .0004, and .0153 respectively). Overall, marital status was statistically significant at examination years 15 and 25 but not in the remaining examinations ($P = .0567$, .0182, .0987, and .0098, respectively; data not shown). Being single was associated with a positive heart age difference at examination years 10 and 25 ($P = .0265$ and .0053, respectively) and being divorced, separated, or widowed was associated positive heart age difference at examination year 15 ($P = .0084$) compared with being married (Table 3).

Longitudinal trends in heart age difference are shown in Table 4. After adjusting for other risk factors, Black participants had on average biological heart ages 4.8 years older than their chronological ages over 15 years of examinations. This difference was highly statistically significant ($P < .0001$). Total cholesterol was associated with −0.01 less years of aging per unit increment ($P = .0415$). UACR and physical activity were associated with 0.32 and −0.45 additional years of aging for each SD increment ($P < .0001$) across the examinations analyzed. Alcohol intake was associated with a 0.02 higher heart age difference ($P < .0001$). Each additional year of education was associated with an average of 0.37 lower years of biological age compared with chronological age, which was statistically significant after adjusting for other risk factors ($P < .0001$). Being single or never married compared with married was associated with greater heart age difference ($P = .0058$), but being divorced was not a significant predictor of heart age difference ($P = .3735$; Table 4).

Table 1
Characteristics of CARDIA cohort and analytic sample at exam year 0

Variable	Entire cohort ($n = 5114$)	Analytic sample ($n = 2264$)
Age, mean (SD), y*	**24.8 (3.7)**	**25.9 (3.1)**
Male, *n* (%)	**2327 (45.5)**	**1006 (44.4)**
Black, *n* (%)*	2637 (51.6)	908 (40.1)
Center, *n* (%)		
Birmingham	1178 (23.0)	530 (23.4)
Chicago	1108 (21.7)	510 (22.5)
Minneapolis	1402 (27.4)	619 (27.3)
Oakland	1426 (27.9)	605 (26.7)
Education, mean (SD), y*	13.8 (2.3)	14.4 (2.2)
Marital status, *n* (%)*		
Married/cohabiting	1137 (22.3)	607 (26.8)
Single	3530 (69.1)	1456 (64.4)
Separated/divorced/widowed	440 (8.6)	199 (8.8)
Physical activity, mean (SD), exercise units	420.1 (300.7)	419.2 (297.3)
Alcohol, mean (SD), mL/d	12.1 (22.0)	11.9 (19.6)
Current smoker, *n* (%)*	**1546 (30.5)**	**547 (24.3)**
Diabetes, *n* (%)	**43 (0.9)**	**20 (0.9)**
Hypertension medication, *n* (%)	**115 (2.3)**	**46 (2.0)**
Systolic blood pressure, mean (SD), mm Hg*	**110.4 (10.9)**	**110.0 (10.7)**
Body mass index, mean (SD), kg/m^2	**24.5 (5.0)**	**24.4 (4.7)**
Total cholesterol, mean (SD), mg/dL	176.7 (33.5)	177.7 (32.5)
HDL-C, mean (SD), mg/dL	53.2 (13.2)	53.3 (12.8)
LDL-C, mean (SD), mg/dL	109.1 (31.2)	110.0 (30.4)

Variables in bold are in the heart age calculator.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
* Variables that were statistically significantly different in participants who were and were not included in the analytic sample ($P < .05$).

Discussion

Black participants, men, and those with lower levels of education had positive heart age differences, which correspond to higher

Table 2
Cross-sectional biological and lifestyle risk factors in CARDIA for examination year 10 through year 25

Variable	Year 10	Year 15	Year 20	Year 25
Chronological age, mean, y	**35.9**	**41.0**	**46.0**	**50.9**
Biological heart age, mean, y	35.4	42.0	49.7	53.1
Heart age difference, mean, y	-0.6	1.0	3.7	2.2
Education, mean, y	15.0	15.2	15.2	15.3
Marital status, %				
Married/cohabiting	54.7	62.5	65.5	64.6
Single	29.5	20.0	16.6	15.1
Separated/divorced/widowed	15.8	17.4	18.0	20.4
Physical activity, mean (SD), exercise units	337.4	351.8	346.6	346.2
Alcohol, mean, mL/d	10.7	10.7	11.5	11.9
Current smoker, %	**21.5**	**18.7**	**16.8**	**14.4**
Diabetes, %	**2.1**	**3.1**	**8.7**	**11.9**
Hypertension medication, %	**2.6**	**7.1**	**16.9**	**27.1**
Systolic blood pressure, mean, mm Hg	**109.2**	**112.7**	**116.3**	**119.5**
Body mass index, mean, kg/m^2	**27.2**	**28.4**	**29.2**	**29.7**
Total cholesterol, mean, mg/dL	178.8	185.1	186.3	192.9
Urine albumin/creatinine ratio, mean, mg/g	13.2	14.3	12.8	12.0

Variables in bold are in the heart age calculator.

biological heart age relative to their actual age. The results of these analyses are consistent with previous findings in BRFSS [2], *National Health and Nutrition Examination Survey* [7], and other analyses of the prevalence of cardiovascular risk factors in the United States [8–10]. Of particular importance, these analyses support the presence of the persistent racial disparities in CVD risk present in the United States.

Additionally, these analyses demonstrated that biomarkers of disease states and lifestyle factors not included in the Framingham cardiovascular risk calculator were associated with positive heart age differences. Although these risk factors did not directly contribute to the excess heart age, the results suggest that subpopulations within the analytical sample had different risk profiles.

At year 10, the mean SBP, which is present in the Framingham risk score, and mean total cholesterol, which is not present in the nonlaboratory Framingham CVD risk equation, were not in ranges considered abnormal [11,12]. However, these risk factors remain associated with excess heart age. Together these findings suggest targeting individual biological risk factors might not be sufficient to reduce biological heart age and cardiovascular risk or that there is a continuum of risk within the range of values considered normal.

We observed an unexpected finding in longitudinal analyses that total cholesterol was inversely associated with heart age difference. In cross-sectional analyses, total cholesterol was positively associated with heart age difference at examination years 10 and 15. At examination year 20, this association was not statistically significant. By examination year 25, total cholesterol was inversely related to heart age difference, which appears to drive the significant inverse association in the longitudinal analyses. Neither the Framingham risk score nor the models presented were adjusted for lipid-lowering medication use, which increased from less than 1% in all race and sex subgroups at examination year 10 to between 10.4% for White women and 20.0% for White men at examination year 25. In addition, by examination year 25, these medications were more likely to be the highly effective HMG-CoA reductase inhibitor class rather than older, less effective medications. Previous analyses of CARDIA data showed that lipid-lowering medication use and obesity, which were present in the Framingham risk score, had opposing relationships with mean total cholesterol over time resulting in stable or lower total cholesterol throughout examinations [13].

The ability to clearly communicate cardiovascular risk is important in clinical settings. Absolute risk, as presented in Framingham and other risk scores, may be difficult for individuals without health backgrounds to understand [14,15]. The use of biological heart age compared with risk score to characterize and inform individual risk of CVD demonstrated greater improvement in risk scores in a trial on motivating changes in lifestyle factors [16]. Therefore, understanding the impact of cardiovascular risk factors on biological heart age may improve the ability to communicate risk [17].

Table 3
Cross-sectional multivariable adjusted biological and lifestyle risk factors associated with heart age difference in CARDIA for examination year 10 through year 25

Variable	Year 10		Year 15		Year 20		Year 25	
	Heart age difference	*P*	Heart age difference	*P*	Heart age difference	*P*	Heart age difference	*P*
Black (compared with White)	2.56	<.0001	3.56	<.0001	4.99	<.0001	4.73	<.0001
Total cholesterol, mg/dL	0.03	<.0001	0.03	<.0001	0.01	.0563	−0.04	<.0001
UACR, mg/g	0.24	.0656	1.46	<.0001	1.45	<.0001	1.83	<.0001
Alcohol, mL/d	0.05	<.0001	0.06	<.0001	0.04	<.0001	0.04	<.0001
PA, mean (SD), exercise units	0.21	.1217	−0.48	.0043	−0.78	.0004	−0.57	.0153
Education, y	−0.54	<.0001	−0.62	<.0001	−0.83	<.0001	−0.77	<.0001
Single*	0.69	.0265	0.71	.0989	1.05	.0777	1.86	.0053
Separated/divorced/widowed*	0.60	.1248	1.22	.0084	0.96	.1062	−0.29	.6237

PA = physical activity.
* Compared with married; estimates after adjusting for all other variables and study center; heart age difference is measured in years; per 1 SD increment, where SD = 135.0, 127.6, 57.2, and 40.1 mg/g for UACR and SD = 269.5, 277.5, 275.4, and 279.5 exercise units for PA at the four examinations, respectively.

Table 4
Adjusted longitudinal trends in biological and social risk factors associated with heart age difference in CARDIA from examination year 10 through year 25

Variable	Univariate		Multivariable	
	Heart age difference	*P*	Heart age difference	*P*
Black (compared with White)	5.61	<.0001	4.79	<.0001
Total cholesterol, mg/dL	−0.01	.0116	−0.01	.0415
UACR, mg/g	0.33	<.0001	0.32	<.0001
Alcohol, mL/d	0.02	<.0001	0.02	<.0001
Physical activity, exercise units	−0.55	<.0001	−0.45	<.0001
Education, y	−0.53	<.0001	−0.37	<.0001
Marital status*				
Single	1.08	<.0001	0.73	.0058
Separated/divorced/widowed	0.58	.0071	0.20	.3735

* Compared with married; estimates after adjusting for all other variables, also adjusted for center and examination year; heart age difference is measured in years; per 1 SD increment, where SD = 98.0 mg/g for UACR and SD = 275.5 exercise units for physical activity.

Limitations

The entire CARDIA cohort had more Black participants (51.6% compared with 40.1%) and fewer never smokers (55.9% compared with 60.7%) than the analytic cohort, which was comprised of participants present at year 10 who also attended the next three study visits. Therefore, the sample analyzed may not be generalizable to the entire cohort. However, the results presented are expected to be conservative.

The Framingham 10-year CVD risk calculator has a maximum biological heart age value of 86. At examination year 25, 73 participants reached the maximum calculated biological heart age. As a result, the true biological heart ages for these individuals may be underestimated. In addition, current blood pressure guidelines suggest a target SBP below the value considered normal in the calculator [11]. Finally, in the calculator, continuous risk factors were modeled as linear variables in the model.

Strengths

CARDIA is a longitudinal cohort with high participant retention. Participants were enrolled as young adults and have been followed through middle age. Variable ascertainment within study visits is also high. Biomarkers and risk factors were assessed at all study visits using standard protocols. Direct measurement of SBP and diabetes are also more accurate than self-report, which improves our analyses relative to previous analysis using BRFSS data. Overall, the study methods provide very good quality data.

Conclusions

These analyses of a population-based cohort demonstrated that overall, biological heart age exceeds chronological heart age in a sample of young and middle-aged adults. During examination years 10, 15, 20, and 25%, 34.9%, 43.1%, 53.9%, and 45.6%, respectively, of the available cohort had biological heart ages that exceeded their chronological age. Across all examination years examined here, 62.5% of participants had a positive heart age difference.

Modifiable risk factors, both in the Framingham risk calculator and additional risk factors examined in these analyses, offer an opportunity to potentially reduce biological age. These analyses show that in a sample of Black and White men and women, average biological heart age exceeds chronological age when individuals are in their early 40s. These results emphasize the importance of prevention before this transition. Overall, biological heart age provides valuable information about cardiovascular health using easy-to-obtain variables that can be obtained at home or in clinical settings.

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