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FEATURED ARTICLE

Race, sex, and mid-life changes in brain health: Cardia MRI substudy

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Abstract

Objective: To examine longitudinal race and sex differences in mid-life brain health and to evaluate whether cardiovascular health (CVH) or apolipoprotein E (*APOE*) ε4 explain differences.

Methods: The study included 478 Black and White participants (mean age: 50 years). Total (TBV), gray (GMV), white (WMV), and white matter hyperintensity (WMH) volumes and GM–cerebral blood flow (CBF) were acquired with 3T-magnetic resonance imaging at baseline and 5-year follow-up. Analyses were based on general linear models.

Results: There were race x sex interactions for GMV (*P*-interaction = .004) and CBF (*P*-interaction = .01) such that men showed more decline than women, and this was most evident in Blacks. Blacks compared to Whites had a significantly greater increase in WMH (*P* = .002). All sex–race differences in change were marginally attenuated by CVH and *APOE* ε4.

Conclusion: Race–sex differences in brain health emerge by mid-life. Identifying new environmental factors beyond CVH is needed to develop early interventions to maintain brain health.

KEYWORDS
brain health, cardiovascular health, magnetic resonance imaging, race, sex

1 | BACKGROUND

Atrophy of brain tissue, white matter disease, and lower cerebral blood flow (CBF) are adverse sentinel cerebral changes that precede dementia.[1,2] Studies of older persons suggest sex and race differences in the prevalence of these brain changes[3–7] and the likelihood of developing dementia.[8–11]

To meet national goals to prevent dementia, studies are needed to prospectively document early changes in brain health and to identify those who may be at risk for later cognitive impairment.[12] A growing body of evidence suggests that preventable cardiovascular risk factors are associated with an increase in white matter hyperintensities (WMH),[4,6] cerebral atrophy, cerebral hypoperfusion,[13] and dementia.[14] Differences in mid-life cardiovascular risk[15,16] by race and sex/gender are well known and may explain differences in brain health at an older age. Additionally, there may be differences in the frequency or biologic context of the apolipoprotein E (*APOE*) ε4 allele,[12,17] a genetic susceptibility risk factor for dementia.

There are few prospective studies that can examine early race and sex differences in brain health. Based on a bi-racial community-based cohort, we examine these differences in 5-year change in magnetic resonance imaging (MRI) markers of brain health, and whether the burden of cardiovascular risk factors accounts for these differences. In secondary analyses, we investigated whether presence of *APOE* ε4 modifies race–sex differences in brain health, and whether differences are reflected in cognitive function. Given differences in the burden of cardiovascular risk factors and *APOE* ε4 carriership, we hypothesize differences among sex–race groups in brain health.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (PubMed) sources. While there have been publications on race and sex differences in adverse brain changes that precede dementia, that is, cerebral atrophy, white matter disease, and lower cerebral blood flow (CBF), early midlife data are scarce.
2. **Interpretation**: Our findings demonstrate that men showed more decline than women in gray matter volume and CBF, and this was most evident in Blacks. Blacks compared to Whites had a significantly greater increase in white matter hyperintensities. All sex–race differences in change were marginally attenuated by cardiovascular health (CVH) and apolipoprotein E ε4.
3. **Future directions**: To further understand the race and sex differences in mid-life brain health, new environmental factors beyond CVH need to be identified. To establish divergent trajectories of mid-life brain health decline by race and sex can identify high-risk groups to target for early preventative strategies to reduce dementia risk.

2 | METHODS

2.1 | Study population

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a bi-racial longitudinal study initiated to investigate the development and determinants of (sub) clinical cardiovascular disease beginning in young adulthood.[18] Black and White participants between the ages of 18 and 30 years were recruited from four sites in the United States in 1985/1986 to achieve a balanced distribution by sex, age, education, and race. The CARDIA Brain MRI substudy targeted 700 individuals balanced by sex and race and recruited from three CARDIA field centers (Birmingham, Alabama; Minneapolis, Minnesota; Oakland, California) at the 25-year follow-up in 2010/2011 (mean participant age = 50.4 [standard deviation (SD) 3.5] years, range 43–56 years) and repeated 5.0 years (SD 0.42 years) later. Exclusion criteria included MRI contraindications or a body size too large for the MRI scanner.

2.2 | Standard protocol approvals, registrations, and patient consents

The MRI protocol for the CARDIA Brain MRI Substudy was approved by the institutional review boards of the University of Alabama Birmingham, the University of Minnesota, Kaiser Permanente Northern California (KPNC), the University of Pennsylvania, and the National Institutes of Health Office of Human Subjects Research Protection for the Intramural Research Program, National Institute on Aging. All participants signed a separate written informed consent for the CARDIA Brain MRI Substudy.

2.3 | MRI acquisition and processing

Multimodal brain MRI scans were acquired on 3T MRI scanners (including a Siemens 3T Tim Trio [VB 15 platform] scanner at the Minneapolis and Oakland and a Philips 3T Achieva [2.6.3.6 platform]) scanner in the Birmingham center. At each MRI field center, trained technologists followed standard quality assurance protocols, including scanning of phantoms previously developed for the Function Biomedical Informatics Research Network and the Alzheimer's Disease Neuroimaging Initiative. The CARDIA MRI protocol consists of sagittal T1, T2, and fluid-Attenuated inversion recovery (FLAIR) to assess volumes and pseudo-continuous arterial spin labeling (pCASL) to assess CBF. Appendix A provides a description of MRI acquisition and image analyses, which have been previously described.[19–21]

In this analysis, we examined volumes of total brain (TBV), total gray matter (GMV), total normal white matter (WMV) and abnormal WMV, referred to WMH volume. We report on CBF in GM, as the pCASL sequence is not accurate in WM.[22]

2.4 | Demographics, cardiovascular health, cognition, and *APOE* ε4 covariates

Participant self-identified race (non-Hispanic Black or non-Hispanic White) and sex, as well as education (years) were assessed by questionnaire.[18,23] To examine the effect of cardiovascular health (CVH) on sex and race differences, we chose the American Heart Association's scale of cardiovascular health Life's Simple 7 (CVH-LS7). This scale has been developed as a metric for public health messages about heart health.[24] In cross-sectional analyses, the CVH-LS7 are positively associated with better cognitive test scores[25] and MRI outcomes[26] in the CARDIA cohort. The scale is based on the following: Blood pressure was measured three times 1 minute apart, with a sphygmomanometer (Omron HEM-907XL; Online Fitness) on the right arm of a seated participant; the average of the second and third measurement was used for analysis. Fasting blood was used to obtain fasting glucose, which was measured with hexokinase coupled to glucose-6-phosphate dehydrogenase (Linco Research) and total cholesterol.[27]

Use of medication for high blood pressure, cholesterol, or diabetes was based on self-administered questionnaires.[18] Physical activity, quantified as a score based on the CARDIA Physical Activity History questionnaire, was assessed as the time spent per week in eight vigorous intensity and five moderate intensity sport-related activities over the past year.[28] Smoking status is based on self-report. Body mass index (BMI) calculated from measured body weight and height (kg/m^2). Diet was quantified with the dietary assessment at Y20. This was based on a 28-day food consumption pattern measured with an interviewer-administered diet history questionnaire specifically developed for the CARDIA study.[29,30] Specific coding for the CVH-LS7 is described in Appendix B.[24]

For cognitive analyses, psychomotor speed was assessed by the Digit Symbol Substitution Test (DSST),[31] with higher scores for digits correctly substituted indicating better function. Verbal memory was assessed by the Rey Auditory Verbal Learning Test (RAVLT), with higher scores after a 10-minute delay indicating better function.[32] Executive function was defined by the Stroop interference test, with higher interference scores indicating worse function.[33] ApoE isoform (2,3,4) was determined in plasma collected at the 7-year follow-up exam. This assay, previously describe by Kamboh et al.,[34] has a 96% concordance with genotype.[35]

2.5 | Analytical sample

A total of 488 participants in the CARDIA Brain MRI Substudy had baseline and follow-up MRI scans.[18] For longitudinal volumetric analyses, 10 participants were excluded due to processing failure (either related to image quality or the presence of a structural lesion) leaving 478 participants (Birmingham n = 105, Minneapolis n = 189, Oakland n = 184). Compared to those with two scans, those with only one MRI scan were less likely to have ideal CVH-LS7 levels of smoking, BMI, blood pressure, or glucose and had fewer years of education (Table S1 in supporting information). The Birmingham site had the largest proportion of Black participants, otherwise sex and age distributions were similar across centers (Table S2 in supporting information). For longitudinal CBF analyses, 189 scans acquired at the Minneapolis site were excluded due to technical incompatibilities in pCASL acquisitions at follow-up. After visual inspection of the pCASL, mean CBF maps 29 were excluded due to various artifacts, including failed linear alignment (n = 1), and low quality of CBF data (defined as a score < 0.5 on an empirical threshold for CBF data quality, n = 35), leaving 235 for CBF analyses (59 from Birmingham and 176 from Oakland). See Table S3 in supporting information for final sample sizes of volumetric and CBF measures by race–sex groups.

2.6 | Statistical analyses

Cerebral volumes were expressed in percentage of intracranial volume (GMV+WMV+WMH+ cerebrospinal fluid [ICV]) to correct for head size; CBF is measured as ml/100 g/min. To normalize the distribution of WMH, we applied inverse hyperbolic sine transformation "asinh" $f(x) = \log(x+(x^2+1)^{0.5})$, which is similar to a log transformation but can accommodate values of zero. Sex and race differences in baseline demographic and health characteristics were compared using analysis of variance for continuous and Chi-square for categorical variables. Differences in MRI features between baseline and follow-up were tested with a paired sample *t* test.

Adjusted group differences in change of MRI features were tested using a "residualized change approach" in which the follow-up MRI feature is the dependent variable, and the baseline MRI is included as an independent variable.[36] This model tests the association of sex and race to variation in the follow-up MRI that is unexplained (residuals) by baseline MRI, that is, the variability due to change. Model 1 included sex and race, adjusting for age, center, and education (years). To explore whether race and sex differences were explained by CVH-LS7 factors, we additionally entered into Model 2 each LS7 metric individually and then separately as a composite score where the presence of a healthy metric is given 1 point and summed up, so higher scores mean better CVH. We tested for sex–race interactions by entering into the models the race x sex term.

In secondary analyses, we included the individual metrics that are continuous in Model 2. Because estimates were similar, we present the public-health–relevant CVH-LS7 metrics. In Model 3, we included the presence or absence of the *APOE ε4* allele as a covariate to explore whether this marker of genetic risk for Alzheimer's disease explains sex and race differences.

To explore whether changes in volumes and CBF were related to cognitive function at follow-up, we used the DSST, RAVLT, and Stroop interference scores as the outcomes. These were exploratory analyses in our entire sample with n = 478 participants, as a larger sample size would be needed for reliable detection by each race and sex subgroup separately. Statistical analysis was performed with SPSS software (Build 1.0.0.1298, 64-bit edition) and a *P*-value < .05 was considered statistically significant.

3 | RESULTS

The longitudinal sample (n = 478) included 48.1% male and 38.3% Black participants (Table 1). Mean age (SD) was 50.4 years (3.5) (range 43–56) at baseline and 55.4 (3.5) at follow-up (range 47–61). Compared to the other race and sex groups, Black men least often had ideal CVH-LS7 levels for BMI, blood pressure, and smoking; White men least often had ideal glucose levels. Black women were least likely to have ideal CVH-LS7 levels for physical activity and diet. Black men and women had proportionately more one or two copies of the *APOE ε4* allele. Baseline values for TBV, GMV, and CBF were higher in women compared to men, with Black women having the highest values for all three measures (Table 2).

3.1 | Midlife 5-year changes in brain tissue volumes and GM-CBF

Over the 5-year period between baseline and follow-up, there was a significant adjusted mean (95% confidence interval [CI]) decline in TBV, GMV, and GM-CBF; and marginal changes in WMV and WMH (Table 2).

TABLE 1 Characteristics at baseline by race and sex groups: CARDIA Brain MRI Substudy

	Total		Black male		White male		Black women		White women		
	n = 478		n = 86		n = 144		n = 97		n = 151		*P*
Age, mean (SD)	50.4	3.5	49.5	3.5	51.0	3.3	49.4	3.8	51.0	3.2	<.001
Education, years, mean (SD)	15.1	2.5	13.7	2.4	15.5	2.3	14.3	2.7	16.0	2.3	<.001
1 or 2 *APOE* ε4 alleles, n %	130	29.3	30	39.5	35	25.2	32	36.8	33	23.4	.022
Cardiovascular health metrics at ideal levels, n %											
Body mass index < 25.0 kg/m^2	159	33.3	13	15.3	42	29.2	24	24.7	80	53.0	<.001
Ideal diet*	21	5.4	4	5.9	6	5.2	3	3.7	8	6.3	.87
Smoking: never or quit > 12 months	397	84.1	57	67.1	131	91.0	76	80.9	133	89.3	<.001
Physical activity ≥300 exercise units	247	51.7	42	48.8	93	64.6	33	34.0	79	52.3	<.001
Total cholesterol < 200 mg/dL	242	50.6	55	64.0	66	45.8	44	45.4	77	51.0	.036
Blood pressure SBP < 120/DBP < 80 mmHg	234	49.1	23	26.7	70	48.6	34	35.1	107	71.3	<.001
Fasting glucose < 100 mg/dL	385	80.7	64	74.4	102	70.8	80	82.5	139	92.7	<.001

Abbreviations: *APOE*, apolipoprotein E; CARDIA Coronary Artery Risk Development in Young Adults; DBP, diastolic blood pressure; MRI, magnetic resonance imaging; SBP, systolic blood pressure; SD, standard deviation.
*Fruits and vegetables: ≥ 4.5 servings/d; sodium: < 1,500 mg/day; fish: ≥ 7oz/week; whole grains: ≥ 3 servings/day; and sugar-sweetened beverages: < 32 oz/week.

The crude annualized changes are −0.12 (SD 0.19) % ICV/year for TBV; −0.13 (0.17) %ICV/year for GMV; and −0.57 (1.69) ml/100 g/min/year for GM-CBF.

3.2 | CVH-LS7 and brain health

Accounting for baseline MRI and other Model 1 variables, the total score of LS7 was not associated with any MRI feature (Table S4 in supporting information). However, specific components were associated with specific MRI measures. Compared to current smoking, never or former smoking was associated with larger TBV, GMV, and WMV. Ideal levels for glucose were related to lower WMH volume.

3.3 | Race and sex differences in midlife 5-year changes in brain volume and CBF

Overall, all race–sex groups had some decline in TBV, GMV, and GM-CBF, except for GM-CBF in Black women and White men (Column A, Table 3). There were significant race–sex interactions for GMV (P = .004) and GM-CBF (P = .01; Column B, Table 3). Overall compared to men, women had significantly less decline in TBV (Column C, Table 3). Black compared to White participants had a significantly higher increase in WMH (P = .002; Column D, Table 3). Where there were significant sex–race interactions, we found Black women in particular had significantly less decline in GMV (mean difference, 95% CI −0.36 [−0.57, −0.16] compared to the other race–sex groups. Black men in particular had significantly more decline in GM-CBF than White and Black women (Column E, Table 3). Adjusting for the total CVR-LS7 score (Table S5 in supporting information), or specifically for smoking, blood pressure, and glucose as metrics and as continuous variables (Table S6 in supporting information), or for the presence or absence of an *APOE* ε4 allele (Table S7 in supporting information) marginally attenuated the race–sex differences. A larger increase in WMH was related to a lower DSST score (lower psychomotor speed) and a higher Stroop interference score (worse executive function). More decline in TBV and GMV was related to a higher Stroop interference score (Table S8 in supporting information).

4 | DISCUSSION

In this community-based bi-racial middle-aged (mean 50 years at baseline) cohort, there were race and sex differences in brain health at baseline. After 5 years, there were significant differences by race and sex in the amount of adverse change in MRI features. Specifically, overall, there was a significant decline in TBV, GMV, and GM-CBF as well as a marginal increase in WMH. Compared to women, men had a greater decline in TBV and GMV. Sex differences in GMV and GM-CBF were most pronounced in Blacks. Although there were race–sex differences in CVH-LS7 and in the frequency of the *APOE* ε4 allele, entering these characteristics into our base model did not change results.

There are few longitudinal studies of brain MRI changes in middle-aged bi-racial community-based cohorts. However, cross-sectional data over the life course suggest brain volumes begin an accelerated decline in the sixth decade, suggesting we are capturing change at a critical point when subsequent brain pathology develops.[37]

TABLE 2 Crude change in MRI features per race and sex: CARDIA Brain MRI Substudy

	Baseline		Follow-up		5-year Difference	95% CI			Annualized difference	
	Mean	SD	Mean	SD	Mean	Lower	Upper	*P*	Mean	SD
Total brain volume, %ICV										
Total sample	85.2	2.7	84.6	2.8	−0.59	−0.67	−0.51	<.001	−0.12	0.19
Black male	84.8	2.7	83.9	2.9	−0.89	−1.09	−0.69	<.001	−0.18	0.19
White male	84.4	2.5	83.5	2.5	−0.84	−0.97	−0.72	<.001	−0.17	0.15
Black female	86.7	2.5	86.5	2.6	−0.20	−0.42	0.03	.084	−0.04	0.22
White female	85.1	2.4	84.7	2.6	−0.43	−0.56	−0.30	<.001	−0.09	0.16
Gray matter volume, %ICV										
Total sample	46.9	2.2	46.2	2.4	−0.66	−0.74	−0.59	<.001	−0.13	0.17
Black male	46.1	2.2	45.3	2.3	−0.89	−1.07	−0.71	<.001	−0.18	0.17
White male	46.1	1.9	45.4	2.0	−0.75	−0.86	−0.64	<.001	−0.15	0.13
Black female	48.1	2.3	47.8	2.4	−0.36	−0.57	−0.16	.001	−0.07	0.20
White female	47.1	2.0	46.5	2.1	−0.64	−0.77	−0.51	<.001	−0.13	0.16
White matter volume, %ICV										
Total sample	38.3	1.5	38.4	1.5	0.073	0.020	0.13	.007	0.015	0.12
Black male	38.6	1.3	38.6	1.4	<0.001	−0.10	0.10	.998	←0.001	0.09
White male	38.3	1.6	38.2	1.6	−0.09	−0.17	−0.01	.024	−0.018	0.10
Black female	38.6	1.5	38.8	1.5	0.17	0.02	0.31	.024	0.034	0.14
White female	38.0	1.5	38.2	1.5	0.21	0.12	0.31	<.001	0.043	0.12
WMH volume, %ICV										
Total sample	0.11	0.11	0.12	0.17	0.012	0.003	0.02	.006	0.0024	0.001
Black male	0.12	0.18	0.16	0.27	0.043	0.01	0.07	.006	0.0086	0.003
White male	0.10	0.08	0.09	0.10	−0.0003	−0.01	0.01	.940	←0.001	0.001
Black female	0.13	0.14	0.15	0.23	0.024	−0.005	0.05	.098	0.0050	0.003
White female	0.11	0.07	0.11	0.10	−0.001	−0.01	0.01	.750	−0.0003	0.001
Gray matter CBF, ml/100g/min										
Total sample	44.0	9.5	41.2	8.3	−2.80	−3.88	−1.72	<.001	−0.57	1.69
Black male	42.8	6.7	38.2	5.6	−4.65	−6.46	−2.83	<.001	−0.93	1.23
White male	38.4	7.6	36.8	7.4	−1.53	−3.43	0.37	.112	−0.31	1.56
Black female	49.4	10.5	47.2	7.4	−2.17	−5.15	0.81	.150	−0.46	2.18
White female	46.2	8.9	42.9	8.1	−3.30	−5.28	-1.33	.001	−0.67	1.65

Abbreviations: CARDIA Coronary Artery Risk Development in Young Adults; CBF, cerebral blood flow; CI, confidence interval; FU, follow-up; ICV, intracranial volume; MRI, magnetic resonance imaging; SD, standard deviation; WMH, white matter hyperintensities transformed with asinh function.
Notes: In the Black female group, n = 1 observation was excluded with a drop in CBF from baseline to FU of 48 mL/min/100 g.

Cross-sectional studies also suggest GM tends to atrophy sooner than WM,[38] consistent with the small but significant decline in GMV in our cohort. There was a small but positive increase in WMV, which may be due to minor measurement errors in the automatic segmentation of white matter.

The changes in this middle-aged cohort are relatively modest compared to those with cardiovascular disease or cognitive impairment. For example, in this cohort (mean age 50 years at baseline) TBV declined by 0.118%ICV which over a 20-year period would be 2.36%ICV loss of TBV, assuming a linear decline and relatively good health. However, for instance, the prevalence of type 2 diabetes mellitus (T2DM) is expected to double in the next decades, disproportionately in race–sex groups (https://www.cdc.gov/diabetes/resources-publications/index.htm). In the ACCORD MIND trial of persons with long-standing T2DM (mean age 62),[36] participants had a 4cm^3/year decline in TBV. Further, cognitive trajectories to mild cognitive impairment (MCI) and dementia are nonlinear and can increase exponentially increase by age, affecting more than 30% of people 75 years and older.[39] In the Mayo Clinic Study of Aging, they found 0.8% decline per year in those who converted to MCI or dementia, which reflects underlying brain atrophy, vascular damage, and hypoperfusion.[1,2,40] By establishing a baseline in middle age, with prospective follow-up we will

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TABLE 3 Adjusted change in MRI features by sex, race, and race–sex groups, model 1

	Meandiff*Col A*	95%CI upper	95%CI lower	*P*-per subgroup	*P*-interactrace x sex*Col B*	*P*-sex diff*Col C*	*P*-race diff*Col D*	*P* values race–sexcomparisons*Col E*		
Total brain volume, %ICV										
Total sample	−0.59	-0.67	-0.51	<.001	NS					
Men	−0.85	−0.96	−0.75	<.001						
Women	−0.34	−0.46	−0.22	<.001		<.001				
Black	−0.51	−0.66	−0.36	<.001						
White	−0.63	−0.72	−0.54	<.001			.14			
Black male	−0.87	−1.08	−0.67	<.001				Ref		
White male	−0.84	−0.97	−0.71	<.001				.91	Ref	
Black female	−0.20	−0.42	0.03	.08				<.001	<.001	Ref
White female	−0.43	−0.56	−0.30	<.001				.001	<.001	.03
Gray matter volume, %ICV										
Total sample	−0.66	−0.74	−0.59	<.001	.004					
Men	−0.80	−0.90	−0.71	<.001						
Women	−0.53	−0.65	−0.42	<.001		<.001				
Black	−0.61	−0.75	−0.47	<.001						
White	−0.69	−0.78	−0.61	<.001			.19			
Black male	−0.90	−1.08	−0.71	<.001				Ref		
White male	−0.75	−0.86	−0.64	<.001				.28	Ref	
Black female	−0.36	−0.57	−0.16	.001				<.001	<.001	Ref
White female	−0.64	−0.77	−0.51	<.001				.03	.19	.004
White matter volume, %ICV										
Total sample	0.077	0.03	0.13	.003	NS					
Men	−0.05	−0.11	0.01	.11						
Women	0.19	0.11	0.28	<.001		<.001				
Black	0.10	0.01	0.19	.03						
White	0.06	0.001	0.13	.047			.42			
Black male	0.02	−0.07	0.12	.63				Ref		
White male	−0.09	−0.17	−0.01	.02				.11	Ref	
Black female	0.17	0.02	0.31	.02				.11	.001	Ref
White female	0.21	0.12	0.31	<.001				.048	<.001	.72
WMH volume, %ICV										
Total sample	0.012	0.004	0.020	.005	NS					
Men	0.016	0.004	0.03	.01						
Women	0.008	−0.003	0.02	.17		.11				
Black	0.033	0.013	0.05	.001						
White	−0.001	−0.006	0.004	.76			.002			
Black male	0.044	0.014	0.074	.005				Ref		
White male	−0.0003	−0.01	0.01	.94				.006	Ref	
Black female	0.02	−0.004	0.05	.09				.11	.25	Ref
White female	−0.001	−0.01	0.01	.74				.001	.42	.07
Gray matter CBF, ml/100g/min										
Total sample	−2.75	−3.83	−1.67	<.001	.01					

(Continues)

TABLE 3 (Continued)

	MeandiffCol A	95%CI upper	95%CI lower	P-per subgroup	P-interactrace x sexCol B	P-sex diffCol C	P-race diffCol D	P values race–sexcomparisonsCol E		
Men	−2.63	−3.97	−1.29	<.001						
Women	−2.85	−4.52	−1.18	.001		<.001				
Black	−3.21	−5.00	−1.41	.001						
White	−2.45	−3.80	−1.11	<.001			.16			
Black male	−4.42	−6.24	−2.60	<.001				Ref		
White male	−1.53	−3.43	0.35	.11				.44	Ref	
Black female	−2.17	−5.22	0.89	.16				<.001	<.001	Ref
White female	−3.30	−5.27	−1.34	.001				.003	.012	.007

Abbreviations: CBF, cerebral blood flow; CI, confidence interval; ICV, intracranial volume; MRI, magnetic resonance imaging; WMH, white matter hyperintensities.

Notes: WMH were transformed with inverse hyperbolic sine transformation $f(x) = \log(x+[x^2+1]^{0.5})$. *P*-values for interaction and for comparisons among groups (among sex, race, or race–sex groups) are adjusted for age, center, education, and baseline value of MRI feature (Model 1). Sample size for volumes: n = 478, for cerebral perfusion n = 235.

be able to better identify persons at future risk for dementia. Specifically, our study design mitigates the bias in age of clinical onset and trajectory shape that can be caused by not including into the cohort people who have already started to decline, or including people who have already started to decline (left censoring or truncation).[41]

Studies of similarly designed cohorts of older persons have found some race or sex differences in brain MRI measures. For example, the Cardiovascular Health Study (over 65 years old at baseline) showed men, compared to women, had significantly more decline in total brain volume; race differences were not tested.[42] The ARIC MRI-subsample (baseline age 62 years) showed after 10 years, Blacks had a higher white matter lesion load, with no sex differences. Neither study examined differences by sex–race groups.[43] A large cross-sectional pCASL study in midlife (age range: 30–55 years) showed that men compared to women had significantly lower CBF but did not find race differences.[13]

In addition to when and which subgroups are at risk, the other important question for prevention is whether adverse changes and disparities in these changes can be prevented. To address this question, we explored the effects on the models of adding American Heart Association ideal CVH-LS7 factors. In our subsample, Black compared to White participants were least likely to have some CVH-LS7 ideal levels, consistent with other studies.[15] Previous cross-sectional analyses of the CARDIA MRI Subsample showed a higher CVH-LS7 score was significantly associated with higher TBV.[26] In this longitudinal analysis, the total CVH-LS7 score was not associated with the amount of change in the MRI measures and only partially attenuated race–sex differences. However specific metrics were associated with indicators of brain health including no current smoking (higher TBV, GMV, and WMV) and ideal levels of glucose (smaller increase in WMH). Smoking and diabetes are robustly found to increase the risk for early brain aging[21] and dementia. We did see an inverse association between an ideal level for physical activity and larger decline in CBF that may reflect a race–sex imbalance. Even though we statistically controlled for sex, there may be residual effects that reflect unmeasured exposures captured by these two variables.

Although there is robust evidence that cardiovascular risk factors have a negative impact on the brain, our study suggests CVH-LS7 metrics as proposed do not, in the age of this cohort and the small amount of change, substantially explain early subgroup differences in decline of brain health metrics. Sex and race are concepts that include interactions among many emerging bio-behavioral factors that translate to health differences and that have not yet been systematically studied. This includes influencers such as the socioeconomic environment, mental health, access to health and social services, geospatial neighborhood environments, and institutional racism, all of which have recently been encapsulated into the meta-concept of the "exposome."[44,45] Additionally, the observed sex differences in brain health may be due to sex-specific differences that affect gene expression patterns, hormonal balance,[46] vascular health,[47] the gut microbiome,[48] or mechanisms related to accelerated aging.[49]

This study contributes to gaps in our knowledge about to whom and when to target prevention interventions to prevent dementia. The strengths of this study include the prospective design, the inclusion of people in the age range that brain health begins to decline, the inclusion of two race/ethnicities living in different regions in the United States, and standardized acquisition of MRI and risk factors.

However, in this context, there are limitations of our study. Although this study is based on a relatively large longitudinal MRI sample, it is limited to those who participated in the CARDIA study 25- and 30-year follow-ups and in both MRI exams. We showed that participants who did not return for follow-up MRI had less favorable CVH-LS7 scores. The reduced sample size affects statistical power and can reflect bias if the associations of the variables of interest differ between those who did and did not participate in the follow-up. When interpreting these data, it is also important to consider our approach to risk factor definition. We used one timepoint measured at the baseline MRI exam, and we expressed the risk factors in a clinically positive way as a total score of CVH metrics shown maintain cardiovascular health. Based on this study of people in their 50s, a focus on a single health metric targeted to the individual needs may be more effective than using composite

scores to guide effective reduction of future risk.[26] Finally, this study is based on two MRI timepoints and we studied macroscopic changes in the brain. To prospectively establish divergent trajectories of brain health, robust markers of developing brain pathology are needed to be measured early in the life course, and more frequently to achieve the goal of identifying effective early prevention approach to reduce the risk of devastating late-life dementias.

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CONFLICTS OF INTEREST

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APPENDIX A

MRI acquisition

CARDIA MRI protocol consists of: (1) Sagittal T1-weighted 3D magnetization-prepared rapid gradient echo (MPRAGE) data acquired with TR/TE/TI = 1900/2.9/900 ms, flip angle = 9^0, bandwidth = 170 Hz/pixel, voxel size = 1 × 1 × 1 mm, matrix = 256 × 256, slices = 176. (2) Sagittal T2 weighted MRI was obtained with TR/TE = 3200/409 ms, bandwidth = 750 Hz/pixel, voxel size = 1 × 1 × 1 mm, matrix = 258 × 256, slices = 176. (3) Sagittal FLAIR MRI acquired with TR/TE/TI = 6000/160/2200 ms, bandwidth = 930 Hz/px, voxel size = 1 × 1 × 1 mm, matrix = 258 × 221, slices = 160. (4) Non-background suppressed 2D pCASL data acquired with gradient-echo echoplanar imaging (EPI) with TR/TE = 4000/11 ms, voxel size = 3.4 × 3.4 × 5 mm^3, matrix = 64 × 64, flip angle = 90 degree, FOV = 220 × 220 mm^2, bandwidth = 3004 Hz/pixel, echo spacing = 0.44 ms and EPI factor = 64. Twenty slices with a distance factor of 20% were acquired from inferior to superior in a sequential order. The labeling was performed with a labeling duration of 1.48 s, post labeling delay (PLD) = 1.5 s at 9 cm below the center of the imaging volume. 40 label/control pairs were acquired for signal averaging.

MRI post-processing

MRI data were transferred to a central archive and processed at the CARDIA MRI Reading Center at the University of Pennsylvania using an automated pipeline. Images with incidental findings, motion artifacts, or poor image quality affecting image processing were excluded from analyses.

Structural MR images were processed using a previously described automated multispectral computer algorithm. After correction of intensity inhomogeneities[50] a multi-atlas skull stripping algorithm was applied to remove extra-cranial tissues.[51] Each T1-weighted scan was automatically segmented into a set of anatomical regions of interest (ROIs) using a multi-atlas label fusion method, MUSE.[52] WMH were segmented from FLAIR images using an automated Deep Learning method that was trained and validated on 3T scans. Volumes of normal and abnormal brain tissues were calculated within specific anatomic regions of interest of the cerebrum. Regions of interest for this paper were volumes of total GM, normal WM, abnormal white matter hyperintensities (WMH), TBV (the sum of GM, WM, and WMH) and ICV, a measure of head size, was estimated as the sum of GM, WM, WMH, and cerebrospinal fluid, based on T2 images, which have high contrast between the high signal in cerebrospinal fluid and low signal in the skull. pCASL processing followed the recommendation by Alsop et al. and is previously described by Dolui.[53] Processing included motion correction, CBF quantification, and subsequent denoising based on a structural correlation with robust Bayesian criteria.[54] We report CBF in GM as pCASL is known to have a lower accuracy in WM.[55]

APPENDIX B

Ideal levels of the American Heart Association (AHA) Life's Simple 7 (LS7) cardiovascular health metrics were defined as: never smoking or quit > 12 months; BMI < 25.0 kg/m^2; physical activity at goal levels of ≥300 exercise units (representing 30 minutes of moderate physical activity 5 times/week); untreated total cholesterol < 200 mg/dL; untreated systolic/diastolic blood pressure < 120/ < 80 mm Hg; untreated fasting blood glucose < 100 mg/dL; and diet consistent with current guideline recommendations. Ideal diet was defined as having at least four of the following five components: fruits and vegetables: ≥ 4.5 servings/d; sodium: < 1,500 mg/day; fish: ≥7 oz/week; whole grains:

≥ 3 servings/day; and sugar-sweetened beverages: < 32 oz/week. Values for participants with an extreme energy intake (defined as < 800 or > 8000 kcal/day for men and < 600 or > 6000 kcal/day for women) were set to missing. The total score ranges from 0 (no metric at ideal level) to 7 (all metrics at ideal levels).

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REFERENCES

1. West NA, Windham BG, Knopman DS, Shibata DK, Coker LH. Neuroimaging findings in midlife and risk of late-life dementia over 20 years of follow-up. *Neurology*. 2019;92:e917-e23.
2. Wolters FJ, Zonneveld HI, Hofman A, et al. Cerebral perfusion and the risk of dementia: a population-based study. *Circulation*. 2017;136:719-728.
3. Apostolova LG, Dinov ID, Dutton RA, et al. 3D comparison of hippocampal atrophy in amnestic mild cognitive impairment and Alzheimer's disease. *Brain*. 2006;129:2867-2873.
4. Brickman AM, Schupf N, Manly JJ, et al. Brain morphology in older African Americans, Caribbean Hispanics, and whites from northern Manhattan. *Arch Neurol*. 2008;65:1053-1061.
5. Carmichael OT, Kuller LH, Lopez OL, et al. Acceleration of cerebral ventricular expansion in the Cardiovascular Health Study. *Neurobiol Aging*. 2007;28:1316-1321.
6. Liao D, Cooper L, Cai J, et al. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. *Neuroepidemiology*. 1997;16:149-162.
7. Liu W, Lou X, Ma L. Use of 3D pseudo-continuous arterial spin labeling to characterize sex and age differences in cerebral blood flow. *Neuroradiology*. 2016;58:943-948.
8. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9:119-128.
9. Mielke MM, Vemuri P, Rocca WA. Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. *Clin Epidemiol*. 2014;6:37-48.
10. Steenland K, Goldstein FC, Levey A, Wharton W. A meta-analysis of Alzheimer's disease incidence and prevalence comparing African-Americans and Caucasians. *J Alzheimers Dis*. 2016;50:71-76.
11. Tang MX, Cross P, Andrews H, et al. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. *Neurology*. 2001;56:49-56.
12. Altmann A, Tian L, Henderson VW, Greicius MD. Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol*. 2014;75:563-573.
13. Jennings JR, Heim AF, Kuan DC, Gianaros PJ, Muldoon MF, Manuck SB. Use of total cerebral blood flow as an imaging biomarker of known cardiovascular risks. *Stroke*. 2013;44:2480-2485.
14. Whitmer RA, Sidney S, Selby J, Johnston SC, Yaffe K. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*. 2005;64:277-281.
15. Kulshreshtha A, Vaccarino V, Judd SE, et al. Life's Simple 7 and risk of incident stroke: the reasons for geographic and racial differences in stroke study. *Stroke*. 2013;44:1909-1914.
16. Osibogun O, Ogunmoroti O, Tibuakuu M, Benson EM, Michos ED. Sex differences in the association between ideal cardiovascular health and biomarkers of cardiovascular disease among adults in the United States: a cross-sectional analysis from the multiethnic study of atherosclerosis. *BMJ Open*. 2019;9:e031414.
17. Hsu M, Dedhia M, Crusio WE, Delprato A. Sex differences in gene expression patterns associated with the APOE4 allele. *F1000Res*. 2019;8:387.
18. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol*. 1988;41:1105-1116.
19. Alsop DC, Detre JA, Golay X, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magn Reson Med*. 2015;73:102-116.
20. Dolui S, Wang Z, Wang DJJ, et al. Comparison of non-invasive MRI measurements of cerebral blood flow in a large multisite cohort. *J Cereb Blood Flow Metab*. 2016;36:1244-1256.
21. Launer LJ, Lewis CE, Schreiner PJ, et al. Vascular factors and multiple measures of early brain health: cARDIA brain MRI study. *PLoS One*. 2015;10:e0122138.
22. van Gelderen P, de Zwart JA, Duyn JH. Pittfalls of MRI measurement of white matter perfusion based on arterial spin labeling. *Magn Reson Med*. 2008;59:788-795.
23. Forrester S, Jacobs D, Zmora R, Schreiner P, Roger V, Kiefe CI. Racial differences in weathering and its associations with psychosocial stress: the CARDIA study. *SSM Popul Health*. 2019;7:003-003.
24. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation*. 2010;121:586-613.
25. Reis JP, Loria CM, Launer LJ, et al. Cardiovascular health through young adulthood and cognitive functioning in midlife. *Ann Neurol*. 2013;73:170-179.
26. Bancks MP, Allen NB, Dubey P, et al. Cardiovascular health in young adulthood and structural brain MRI in midlife: the CARDIA study. *Neurology*. 2017;89:680-686.
27. Bild DE, Jacobs DR, Liu K, et al. Seven-year trends in plasma low-density-lipoprotein-cholesterol in young adults: the CARDIA Study. *Ann Epidemiol*. 1996;6:235-245.
28. Jacobs DR Jr, Hahn LP, Haskell WL, Pirie P, Sidney S. Validity and Reliability of Short Physical Activity History: cardia and the Minnesota Heart Health Program. *J Cardiopulm Rehabil*. 1989;9:448-459.
29. Liu K, Slattery M. A study of the reliability and comparative validity of the cardia dietary history. *Ethn Dis*. 1994;4:15-27.
30. McDonald A, Van Horn L, Slattery M, et al. The CARDIA dietary history: development, implementation, and evaluation. *J Am Diet Assoc*. 1991;91:1104-1112.
31. Wechsler D, Marion MDL. Wechsler adult intelligence scale-revised. 1988:94-104.
32. Lezak MDHD, Loring DW. *Neuropsychological Assessment*, 4th Edition New York, NY: Oxford University Press. 2004.
33. Houx PJ, Jolles J, Vreeling FW. Stroop interference: aging effects assessed with the Stroop Color-Word Test. *Experimental aging research*. 1993;19:209-224.

34. Kamboh MI, Ferrell RE, Kottke B. Genetic studies of human apolipoproteins. V. A novel rapid procedure to screen apolipoprotein E polymorphism. *J Lipid Res*. 1988;29:1535-1543.
35. Kataoka S, Paidi M, Howard BV. Simplified isoelectric focusing/immunoblotting determination of apoprotein E phenotype. *Clin Chem*. 1994;40:11-13.
36. Launer LJ, Miller ME, Williamson JD, et al. Effects of intensive glucose lowering on brain structure and function in people with type 2 diabetes (ACCORD MIND): a randomised open-label substudy. *Lancet Neurol*. 2011;10:969-977.
37. Habes M, Pomponio R, Shou H, et al. The Brain Chart of Aging: machine-learning analytics reveals links between brain aging, white matter disease, amyloid burden, and cognition in the iSTAGING consortium of 10,216 harmonized MR scans. *Alzheimers Dement*. 2021;17:89-102.
38. Jernigan TL, Archibald SL, Fennema-Notestine C, et al. Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiol Aging*. 2001;22:581-594.
39. Knopman DS, Gottesman RF, Sharrett AR, et al. Mild cognitive impairment and dementia prevalence: the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). *Alzheimers Dement (Amst)*. 2016;2:1-11.
40. Jack CR Jr, Shiung MM, Gunter JL, et al. Comparison of different MRI brain atrophy rate measures with clinical disease progression in AD. *Neurology*. 2004;62:591-600.
41. Cain KC, Harlow SD, Little RJ, et al. Bias due to left truncation and left censoring in longitudinal studies of developmental and disease processes. *Am J Epidemiol*. 2011;173:1078-1084.
42. Coffey CE, Lucke JF, Saxton JA, et al. Sex differences in brain aging: a quantitative magnetic resonance imaging study. *Arch Neurol*. 1998;55:169-179.
43. Knopman DS, Penman AD, Catellier DJ, et al. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. *Neurology*. 2011;76:1879-1885.
44. Tishkoff SA, Kidd KK. Implications of biogeography of human populations for 'race' and medicine. *Nat Genet*. 2004;36:S21-7.
45. Yudell M, Roberts D, DeSalle R, Tishkoff S. SCIENCE AND SOCIETY. Taking race out of human genetics. *Science*. 2016;351:564-565.
46. Lentini E, Kasahara M, Arver S, Savic I. Sex differences in the human brain and the impact of sex chromosomes and sex hormones. *Cereb Cortex*. 2013;23:2322-2336.
47. Krause DN, Duckles SP, Pelligrino DA. Influence of sex steroid hormones on cerebrovascular function. *J Appl Physiol*. 2006;101:1252-1261 (1985).
48. Spichak S, Bastiaanssen TFS, Berding K, et al. Mining microbes for mental health: Determining the role of microbial metabolic pathways in human brain health and disease. *Neurosci Biobehav Rev*. 2021;125:698-761.
49. Lopez-Otin C, Kroemer G. Hallmarks of Health. *Cell*. 2021;184:33-63.
50. Tustison NJ, Avants BB, Cook PA, et al. N4ITK: improved N3 bias correction. *IEEE Trans Med imaging*. 2010;29:1310-1320.
51. Doshi J, Erus G, Ou Y, Gaonkar B, Davatzikos C. Multi-atlas skull-stripping. *Acad Radiol*. 2013;20:1566-1576.
52. Doshi J, Erus G, Ou Y, et al. MUSE: MUlti-atlas region Segmentation utilizing Ensembles of registration algorithms and parameters, and locally optimal atlas selection. *Neuroimage*. 2016;127:186-195.
53. Dolui S, Wang Z, Shinohara RT, Wolk DA, Detre JA. Structural Correlation-based Outlier Rejection (SCORE) algorithm for arterial spin labeling time series. *J. Magn Reson Imaging*. 2017;45:1786-1797.
54. Alsop DC, Detre JA, Golay X, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magn Reson Med*. 2015;73:102-116.
55. Dolui S, Wang Z, Wang DJJ, et al. Comparison of non-invasive MRI measurements of cerebral blood flow in a large multisite cohort. *J Cereb Blood Flow Metab*. 2016;36:1244-1256.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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