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Cardiorespiratory fitness and brain volume and white matter integrity

The CARDIA Study

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ABSTRACT

Objective: We hypothesized that greater cardiorespiratory fitness is associated with lower odds of having unfavorable brain MRI findings.

Methods: We studied 565 healthy, middle-aged, black and white men and women in the CARDIA (Coronary Artery Risk Development in Young Adults) Study. The fitness measure was symptom-limited maximal treadmill test duration (Max_{dur}); brain MRI was measured 5 years later. Brain MRI measures were analyzed as means and as proportions below the 15th percentile (above the 85th percentile for white matter abnormal tissue volume).

Results: Per 1-minute-higher Max_{dur}, the odds ratio for having less whole brain volume was 0.85 ($p = 0.04$) and for having low white matter integrity was 0.80 ($p = 0.02$), adjusted for age, race, sex, clinic, body mass index, smoking, alcohol, diet, physical activity, education, blood pressure, diabetes, total cholesterol, and lung function (plus intracranial volume for white matter integrity). No significant associations were observed between Max_{dur} and abnormal tissue volume or blood flow in white matter. Findings were similar for associations with continuous brain MRI measures.

Conclusions: Greater physical fitness was associated with more brain volume and greater white matter integrity measured 5 years later in middle-aged adults. *Neurology*® 2015;84:1–7

GLOSSARY

ATV = abnormal tissue volume; **CARDIA** = Coronary Artery Risk Development in Young Adults; **CI** = confidence interval; **CRF** = cardiorespiratory fitness; **FA** = fractional anisotropy; **FLAIR** = fluid-attenuated inversion recovery; **ICV** = intracranial volume; **Max_{dur}** = maximal duration; **MS** = multiple sclerosis; **NTV** = normal tissue volume; **OR** = odds ratio; **WBV** = whole brain volume.

Cardiorespiratory fitness (CRF), measured by treadmill duration, correlates with reduced cardiovascular diseases and overall mortality rates.[1–3] Since CRF level may be improved, especially by physical activity and weight loss,[4,5] CRF could be used as an intervention to promote health.

Brain atrophy (low brain tissue volume) in whole brain or certain regions, and white matter findings on brain MRI, including lower volume, fluid-attenuated inversion recovery (FLAIR)/T2 hyperintensity lesions, and reduced integrity as reflected by low fractional anisotropy (FA), have been associated with normal aging, cerebral small vessel disease, hypertension, impaired cognitive function, and Alzheimer disease.[6–19] Recent studies showed that higher CRF was associated with higher whole brain volume (WBV), higher white matter volume and integrity (focal FA values), and higher cerebrovascular reserve in people with Alzheimer disease or multiple sclerosis (MS) and in elders.[20–27] Therefore, we proposed to investigate the associations between CRF and WBV, and especially white matter measurements in black and white study participants to better understand the pathogenesis of brain atrophy and white matter lesions in middle adulthood. We hypothesized that greater CRF, defined by longer symptom-limited maximal treadmill test duration (Max_{dur}), would be associated with lower odds of unfavorable brain MRI findings including less WBV, less normal tissue volume (NTV), more abnormal tissue volume (ATV), and lower integrity and blood flow in white matter in healthy middle-aged adults.

Supplemental data at Neurology.org

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METHODS **Study design.** CARDIA (Coronary Artery Risk Development in Young Adults) is a prospective cohort of participants randomly recruited in Birmingham, AL, Chicago, IL, and Minneapolis, MN, and the Kaiser Permanente Medical Care Plan in Oakland, CA, to study the evolution of cardiovascular risk. Participants were aged 18 to 30 years at enrollment in 1985–1986 and recruitment at baseline was balanced by age, race, sex, and education.[28] At both years 20 and 25, 72% of the surviving cohort were re-examined.[5] Of 710 participants who had brain MRI measured at year 25, 565 also had eligible treadmill tests at year 20 and were analyzed here. Those who did not complete the symptom-limited maximal treadmill test tended to have greater white matter ATV, lower FA, and higher systolic and diastolic blood pressures, but WBV, white matter cerebral blood flow, white matter NTV, and other CVD risk factors, including diabetes and total cholesterol, did not differ from those who completed the treadmill test.

Standard protocol approvals, registrations, and patient consents. The study was approved by the institutional review boards for the protection of human subjects of the participating study. Written informed consent was obtained from all participants at each in-person examination.

Graded exercise testing. The graded symptom-limited maximal exercise test followed a modified Balke protocol of nine 2-minute stages of gradually increasing difficulty.[29] The exposure of interest is Max_{dur}, considered a measure of cardiovascular fitness and a close approximation to physiologic maximum oxygen consumption per minute on a treadmill.[5,30] Participants (n = 127) with ischemic heart disease, concurrent use of any cardiovascular medications except antihypertensive drugs, elevated resting blood pressure before test, or fever were ineligible for the test.[31] General or leg fatigue, shortness of breath, certain medical reasons, or participant refusal to continue were reasons for test termination.[5] Five hundred fifty-eight participants also performed the graded symptom-limited maximal exercise test at year 0.

Brain MRI measurements. The Brain MRI was conducted at Minneapolis, Oakland, and Birmingham at year 25. Structural (T1, T2, and FLAIR), diffusion tensor imaging, and arterial spin labeling imaging sequences were acquired. T1-weighted MRI scans were processed using standardized alignment, removal of extracerebral tissue, and segmentation into gray and white matter to measure the WBV and white matter NTV. A multiparametric automated method, incorporating information from the T1, T2, and FLAIR scans, was applied for white matter lesion segmentation.[32] Each T1 image was automatically parcellated into anatomical regions of interest using a standard template image, using deformable registration.[33] Voxel-wise FA maps were derived from diffusion tensor images using standard methods. In addition, in a subset of 422 participants (Minneapolis and Oakland only), cerebral blood flow was measured using arterial spin labeling images. White matter consists of 13 regions of interest, including frontal lobes, temporal lobes, parietal lobes, occipital lobes, basal ganglia, the corpus callosum, and fornix.

Measurements of other variables. Covariates have been described previously. Details are provided in appendix e-1 on the *Neurology*® Web site at Neurology.org.

Statistical analysis. Assumptions of normal distributions of white matter measurements, and covariates were checked. White matter ATV was strongly right skewed. Given large race and sex differences in Max_{dur}, characteristics were examined across race/sex-specific quartiles of Max_{dur}, with statistical testing using analysis of variance and χ^2 tests. Outcomes of interest were WBV and white matter NTV, ATV, integrity represented by FA, and blood flow. WBV and white matter NTV and ATV were standardized by dividing each by the intracranial volume (ICV). Missing covariates were replaced with race/sex-specific means for continuous variables and values at the closest visit for categorical variables. Multiple linear regressions with brain MRI measurements as continuous variables were conducted to investigate the associations between CRF and brain MRI. To further investigate the association of CRF with unfavorable MRI variables, we dichotomized brain MRI measurements. Low WBV, low white matter NTV, low white matter FA, and low white matter blood flow were defined as ≤15th percentile of the sample values. High ATV was defined as ≥85th percentile. Logistic regression was applied to assess the associations between Max_{dur} and these unfavorable brain MRI measurements. Age, race/sex groups, center, body mass index, smoking status (current, former, never), alcohol intake, diet pattern, physical activity, education, systolic and diastolic blood pressure, diabetes, total cholesterol, and lung function, all at year 20, were adjusted for. Analyses of white matter FA and blood flow in model 2 and model 3 also adjusted for ICV. We also conducted sensitivity analysis with unfavorable MRI measurements defined by the extreme 25th percentile. Interactions between Max_{dur} and race/sex groups on MRI measurements were tested with 3-*df* χ^2 tests. To minimize multiple comparison issues, only the consistency of direction of the odds ratios (ORs) of the association between CRF and brain MRI was considered within the 13 individual regions of interest in white matter; we reported confidence intervals (CIs) for information, but no significance tests were conducted for individual areas.

Statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC). Two-sided tests with type I error (α) of 0.05 were applied.

RESULTS Participants were mean (SD) age 45.5 (3.5) years at year 20. Among them, 92 (16.3%) were black men, 116 (20.5%) were black women, 166 (29.4%) were white men, and 191 (33.8%) were white women. The cohort was apparently healthy regarding lifestyle and clinical measures at year 20 except for mean body mass index of 28.2 kg/m^2 (table 1). Max_{dur} differed significantly across race/sex groups ($p < 0.001$): 7.6 (2.7) minutes for all participants; highest for white men (9.6 [2.2]) and lowest for black women (5.2 [2.1]). Significant differences in characteristics were observed across race/sex-specific quartiles of Max_{dur}. Those who were more fit were more likely to be better educated, thinner, nonsmokers, and physically active. They watched less TV, had a higher quality diet and lower blood pressure, and were less likely to be diabetic (table 1). Those with higher Max_{dur} had larger WBV and white matter NTV, and higher white matter FA (table 1).

In those with unfavorable WBV and white matter FA, after adjustment for age, race, and sex, Max_{dur} was lower compared with those who had favorable brain MRI values. Race associations with brain MRI findings were mixed: of the participants in the lowest 15% of white matter FA and NTV, there were more white participants than of those with higher levels, while of the participants in the highest 15% of white matter ATV, there were fewer white participants than in those with low levels. There were no race differences

Table 1 Brain MRI measurements and year 20 characteristics by quartiles of treadmill duration[a]: CARDIA Study

		Maximal treadmill duration				
	All	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	*p* for trend[b]
WBV, % of ICV	81.3 (2.5)	80.8 (3.0)	81.4 (2.4)	81.4 (2.4)	81.7 (2.1)	0.003
White matter NTV, % of ICV	38.4 (2.0)	38.2 (2.4)	38.5 (2.0)	38.4 (1.8)	38.8 (1.8)	0.03
White matter ATV, % of ICV	0.022 (0.008-0.05)	0.026 (0.008-0.06)	0.023 (0.008-0.05)	0.020 (0.007-0.04)	0.022 (0.009-0.04)	0.54
White matter FA	0.307 (0.019)	0.303 (0.019)	0.308 (0.021)	0.307 (0.018)	0.309 (0.017)	0.03
White matter blood flow,[c] mm^3/100 g/min	42.2 (9.4)	41.91 (10.5)	41.5 (9.8)	42.6 (9.0)	42.5 (8.4)	0.50
Demographics						
Age, y	45.5 (3.5)	45.9 (3.4)	45.9 (3.4)	45.4 (3.4)	44.8 (3.5)	0.004
Education, y in school	15.8 (2.4)	15.2 (2.5)	15.5 (2.4)	15.8 (2.5)	16.5 (2.2)	<0.0001
Behaviors						
Smoking status, %						
Never smoker	63.9	57.1	61.7	68.9	67.1	0.003
Former smoker	20.7	19.6	20.6	19.9	22.9	
Current smoker	15.4	23.3	17.7	11.2	10.1	
Alcohol intake, mL/d	12.5 (22.1)	13.4 (29.1)	11.0 (20.6)	14.2 (23.4)	11.2 (12.6)	0.71
Physical activity score, exercise units	300 (172, 536)	216 (102, 387)	241 (148, 396)	300 (180, 538)	500 (311, 745)	<0.0001
TV watching, h/wk	8.2 (10.9)	10.7 (13.2)	10.1 (11.3)	6.9 (8.5)	5.3 (9.5)	<0.0001
Dietary pattern score	63.3 (11.7)	59.6 (11.0)	62.7 (12.0)	63.5 (11.3)	67.2 (11.2)	<0.0001
Biological						
BMI, kg/m^2	28.2 (7.4)	32.0 (7.0)	29.2 (4.7)	27.0 (4.8)	25.1 (10.0)	<0.0001
Forced expiratory volume, 1 s, L	3.1 (0.8)	2.8 (0.7)	3.1 (0.8)	3.2 (0.7)	3.3 (0.8)	<0.0001
Total cholesterol, mg/dL	185.7 (34.7)	179.9 (35.9)	193.4 (34.3)	189.4 (35.6)	179.6 (31.1)	0.66
Diabetes, %	5.3	12.0	2.8	4.6	2.1	0.001
Systolic blood pressure, mm Hg	114.1 (12.6)	116.5 (14.5)	114.5 (12.3)	113.4 (12.6)	112.2 (10.6)	0.004
Diastolic blood pressure, mm Hg	70.9 (10.3)	74.3 (11.3)	72.1 (10.3)	69.2 (10.0)	68.5 (8.5)	<0.0001
Hypertension, %	14.5	30.1	14.9	8.0	6.4	<0.0001

Abbreviations: ATV = abnormal tissue volume; BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults; FA = fractional anisotropy; ICV = intracranial volume; NTV = normal tissue volume; WBV = whole brain volume.
Data are mean (SD), median (interquartile range), or %.
[a] Race/sex-specific quartiles were used with 25th, 50th, 75th percentiles of 6.6, 8.0, 8.8 for black men, 4.0, 4.9, 6.0 for black women, 8.0,10.0, 11.1 for white men, and 6.0, 7.0, 8.9 for white women.
[b] The *t* test and χ^2 test were used to analyze the statistical differences of the baseline characteristics and white matter measurements across race/sex-specific quartiles of maximal duration.
[c] White matter blood flow, n = 422; all other variables, n = 565.

of those in the lowest 15% of WBV and white matter cerebral blood flow as compared with those who had higher values. Of participants in the highest 15% of white matter ATV and in the lowest 15% of white matter cerebral blood flow, more were women; of participants in the lowest 15% of white matter FA, fewer were women. Mean alcohol intake was higher in those with unfavorable WBV, white matter NTV, and FA. Also, those with unfavorably high white matter ATV and low white matter FA watched more TV, while those with unfavorably low WBV had lower forced expiratory volume in the first second. There were more hypertensive participants in those with unfavorably low WBV and high white matter ATV (tables e-1 and e-2).

Per 1 minute higher, Max_{dur} was associated with 0.18% more ICV in WBV (corresponding to 7% of an SD of WBV), 0.11% more ICV in white matter NTV (corresponding to 6% of an SD of white matter NTV), and 0.0009 higher whiter matter FA (corresponding to 5% of an SD of white matter FA) in models adjusted initially for age, race/sex groups, and field center (table 2, model 1), but not associated with white matter ATV and blood flow. The association between Max_{dur} and WBV and white matter NTV remained significant after adjusting for body mass

Table 2 WBV, NTV, ATV, FA, and blood flow in white matter associated with 1-minute-longer duration on treadmill test: CARDIA Study

Model[a]	Slope	SE	p
WBV, % of ICV			
1	0.18	0.05	0.0002[b]
2	0.20	0.06	0.001[b]
3	0.19	0.06	0.001[b]
White matter NTV, % of ICV			
1	0.11	0.04	0.01[b]
2	0.14	0.05	0.005[b]
3	0.13	0.05	0.01[b]
White matter ATV, % of ICV			
1	0.001	0.001	0.26
2	−0.00002	0.001	0.99
3	0.001	0.001	0.58
White matter FA			
1	0.0009	0.0004	0.02[b]
2	0.0008	0.0004	0.07
3	0.0007	0.0004	0.09
White matter blood flow,[c] mm³/100 g/min			
1	0.05	0.20	0.79
2	−0.12	0.24	0.62
3	−0.12	0.25	0.62

Abbreviations: ATV = abnormal tissue volume; CARDIA = Coronary Artery Risk Development in Young Adults; FA = fractional anisotropy; ICV = intracranial volume; NTV = normal tissue volume; SE = standard error; WBV = whole brain volume.
[a] Model 1: adjusted for age, race/sex groups, clinical center. Model 2: additionally adjusted for body mass index, smoking, alcohol consumption, diet, physical activity, and education; adjusted for ICV for white matter FA and blood flow. Model 3: further adjusted for blood pressure, diabetes, total cholesterol, and lung function; adjusted for ICV for white matter FA and blood flow.
[b] Significant values.
[c] White matter blood flow, n = 422; all other variables, n = 565.

index, smoking, alcohol consumption, diet pattern, physical activity, and education (model 2) while the association between Max_{dur} and white matter FA lost its significance. Additional adjustment for clinical measurements including blood pressure, diabetes, total cholesterol, and lung function (model 3) yielded a similar association between Max_{dur} and WBV and white matter NTV.

In multivariable logistic models adjusted initially for age, race/sex groups, and field center (model 1), Max_{dur} was associated with lower odds of low WBV with the OR per 1-minute-higher Max_{dur} of 0.86 (95% CI, 0.76–0.96), and lower odds of low white matter NTV with the OR per 1-minute-higher Max_{dur} of 0.89 (95% CI, 0.79–0.996), but not associated with high white matter ATV, low white matter FA, or low white matter blood flow (table 3). After adjusting for body mass index, smoking, alcohol consumption, diet pattern, physical activity, and education (model 2), the OR of the association between higher Max_{dur} and low WBV became 0.81 (95% CI, 0.70–0.94), and the associations between Max_{dur} and low white matter NTV became nonsignificant. The finding between higher Max_{dur} and low white matter FA was in the expected direction with further adjustment for ICV. Additional adjustment for clinical measurements including blood pressure, diabetes, total cholesterol, and lung function (model 3) yielded similar associations between higher Max_{dur} and low WBV with the OR of 0.85 (95% CI, 0.72–0.996), and between higher Max_{dur} and low FA with the OR of 0.80 (95% CI, 0.65–0.97). Sensitivity analysis with unfavorable MRI measurements defined by the extreme 25th percentile yielded similar findings (data not shown). No significant interactions were identified between Max_{dur} and race/sex groups on brain MRI measurements (all $p > 0.05$ with $df = 3$).

The direction of association of Max_{dur} with low FA was consistent in all 13 regions of interest in white matter with the overall white matter, although some CIs did include 1, consistent with lower precision of each measure in a smaller area of the brain (table e-3). Year 0 Max_{dur} was not associated with these brain MRI measurements.

DISCUSSION In the current period–cross-sectional study, higher CRF measured by Max_{dur} at average age 45 years was associated with more favorable brain MRI measurements 5 years later. Specifically, higher Max_{dur} was associated with higher WBV and white matter NTV and FA independent of demographic variables. In addition, participants with higher Max_{dur} were less likely to have low WBV and low FA as hypothesized irrespective of demographic, lifestyle, and clinical characteristics. Higher CRF was not significantly associated with higher ATV (hyperintensity) or lower blood flow in white matter.

Our findings of the association between CRF and WBV, white matter NTV, and white matter integrity are consistent with previous findings in cross-sectional studies and clinical trials in people with Alzheimer disease and MS, and in healthy older adults.[20–26] In addition, we previously found that higher CRF was related to better cognitive function in participants of the CARDIA Study.[34] Better cognitive function has been observed to relate to white matter integrity in several other large population studies of middle-aged and elderly individuals.[11–14] Although these associations of CRF with cognitive function and of cognitive function with white matter characteristics do not necessarily mean that brain MRI parameters would be better in those with higher or improved treadmill duration, the evidence presented here is consistent with the hypothesis that brain volume and white matter integrity might respond to improved CRF. The stronger and significant association of CRF and integrity after adjustment for adiposity, lifestyles, and risk factors for cardiovascular

Table 3 Low WBV, low NTV, high ATV, low FA, and low blood flow in white matter associated with 1-minute-longer duration on treadmill test: CARDIA Study

Model[a]	OR (95% CI)	p
Low WBV		
1	0.86 (0.76, 0.96)	0.01[b]
2	0.81 (0.70, 0.94)	0.007[b]
3	0.85 (0.72, 0.996)	0.04[b]
White matter low NTV		
1	0.89 (0.79, 0.996)	0.04[b]
2	0.87 (0.75, 1.01)	0.06
3	0.88 (0.75, 1.02)	0.10
White matter high ATV		
1	1.02 (0.90, 1.15)	0.79
2	0.95 (0.82, 1.11)	0.51
3	0.94 (0.80, 1.11)	0.46
White matter low FA		
1	0.87 (0.76, 1.001)	0.05
2	0.83 (0.69, 0.999)	0.049[b]
3	0.80 (0.65, 0.97)	0.02[b]
White matter low blood flow[c]		
1	0.98 (0.85, 1.12)	0.74
2	1.00 (0.85, 1.18)	0.99
3	0.96 (0.81, 1.16)	0.72

Abbreviations: ATV = abnormal tissue volume; CARDIA = Coronary Artery Risk Development in Young Adults; CI = confidence interval; FA = fractional anisotropy; NTV = normal tissue volume; OR = odds ratio; WBV = whole brain volume.
Low WBV, low white matter NTV, low white matter FA, low white matter blood flow mean values lower than 15th percentiles of the sample values; high white matter ATV means values higher than 85th percentile of the sample values.
[a] Model 1: adjusted for age, race/sex groups, clinical center. Model 2: additionally adjusted for body mass index, smoking, alcohol consumption, diet, physical activity, and education; adjusted for intracranial volume for white matter FA and blood flow. Model 3: additionally adjusted for blood pressure, diabetes, total cholesterol, and lung function; adjusted for intracranial volume for white matter FA and blood flow.
[b] Significant values.
[c] White matter blood flow, n = 422; all other variables, n = 565.

disease and brain aging suggests a negative confounding effect and an independent effect of CRF on WBV, especially on white matter integrity. The absence of association between CRF and white matter lesions reflected as ATV in our study may relate to the age and health of our participants and should not be taken to imply that CRF will not relate to ATV in the long run, as ATV increases in these participants.

The observed association between CRF and WBV, white matter NTV, and white matter integrity, independent of other risk factors, may be explained by some underlying mechanisms. One possible mechanism is that higher CRF, corresponding to higher maximal amount of oxygen an individual can use at any time, may represent better oxygen supply to the brain, which is crucial for the brain to maintain its structure and function.[35] Another possible mechanism is that CRF alters brain volume as well as white matter integrity through regulation of cerebral blood flow. Higher CRF has been found to be associated with higher cerebral blood flow,[27] while higher cortical cerebral blood flow was related to higher white matter FA. Low CRF may lead to lethal consequences to brain cells as metabolic demand by local neurons and glial tissue is supported by cerebral blood flow, which suggests the importance of overall blood supply to brain health, especially white matter health.[35–37] Although no association between CRF and white matter blood flow was found here, our analysis was limited because blood flow was not assessed in one field center; the range of blood flow in our study may be limited because the sample of 422 participants from 2 clinics tended to be white, better educated, and more physically active than in those in whom blood flow was not measured.

Given the age of our participants, the definition of low WBV and low NTV, high abnormal tissue, and low integrity (FA) and blood flow in the white matter may not have clinical significance at this point; however, clinical diseases including hypertension, cerebral small vessel disease, dementia, cognitive impairment, stroke, and MS have been found to be related to low white matter volume, high abnormal tissue, and low integrity.[7–10,14,20–22,24] In addition, we found that participants who were defined as the worst 15% in most MRI variables reported drinking more alcohol than others. Because chronic alcohol consumption is known to be related to some irreversible white matter changes,[38,39] it is very likely that the worst 15% MRI findings in our cohort represent some pathologic deterioration of white matter. We believe that the dichotomized outcomes defined in our study may represent subclinical brain MRI changes in an apparently healthy middle-aged population. The corresponding relations of CRF with the continuous white matter variables gave consistent findings.

Some race and sex differences were noted in our study between those with favorable and unfavorable (extreme 15% of the values) MRI measurements in crude analysis. An analysis conducted by our fellow investigators in another CARDIA study showed that in 670 participants, the adjusted means of total brain volume, white matter abnormal tissue volume, and white matter FA were not different in white and African American participants, or men and women.[40]

The population-based sample of healthy middle-aged white and black participants, who completed symptom-limited maximal treadmill tests 5 years before the brain MRI, are the main strengths of our study. The findings of the current study are generalizable because of community-based sampling at baseline, balanced by age, race, sex, and educational achievement, and the inclusion of adults with obesity and smokers. One

limitation of our study is that brain MRI was only conducted at year 25 and not assessed at the baseline examination. Therefore, it is not possible to test the temporality of the association between Max_{dur} and white matter measurements over 5 years of follow-up. CARDIA plans to follow the participants for brain MRI measurements at year 30 to further explore the brain measurements and their changes over time in association with CRF as these participants enter later adulthood. Furthermore, it is impossible to adjust for baseline MRI measurements when studying the potential predictive effect of Max_{dur} on MRI findings 5 years later. Also, because participants with a known contraindication to an MRI examination, including severe claustrophobia, pacemaker, defibrillator, or any foreign metal objects, and those who were unable to fit in an MRI table because of high BMI, were excluded from the MRI examination, our sample may be limited to a slightly healthier subgroup of the CARDIA Study with lower BMI and fewer cardiovascular events. In addition, the effect sizes observed here are relatively small, which might be secondary to our relatively healthy population. However, although some discrepancy was noted for the associations between Max_{dur} and white matter NTV and FA, overall the findings with different methods including across race/sex-specific quartiles, multiple linear regressions, and logistic regression are quite consistent.

We found that greater CRF measured by Max_{dur} with the treadmill test was associated with higher WBV and white matter NTV and integrity 5 years later among apparently healthy middle-aged adults. The results imply that CRF may play a role in the brain structure and function in this population. It is an interesting possibility that improvement in CRF through exercise may prevent or at least delay future WBV and white matter changes in older adulthood.

AUTHOR CONTRIBUTIONS

Dr. Zhu: wrote the manuscript, data analysis. Dr. Jacobs: wrote the manuscript, data analysis, and secured funding. Dr. Schreiner: critical review of the manuscript and secured funding. Dr. Launer: critical review of the manuscript. Dr. Whitmer: critical review of the manuscript. Dr. Sidney: critical review of the manuscript and secured funding. Dr. Demerath: critical review of the manuscript. Dr. Thomas: critical review of the manuscript. Dr. Bouchard: critical review of the manuscript. Dr. He: critical review of the manuscript. Dr. Erus: critical review of the manuscript, provided MRI details. Dr. Battapady: critical review of the manuscript, provided MRI details. Dr. Bryan: critical review of the manuscript.

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DISCLOSURE

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