ORIGINAL RESEARCH

Aortic Stiffness and White Matter Microstructural Integrity Assessed by Diffusion Tensor Imaging: The ARIC-NCS

Jingkai Wei, PhD; Priya Palta, PhD; Michelle L. Meyer, PhD; Anna Kucharska-Newton, PhD; Brian W. Pence, PhD; Allison E. Aiello, PhD; Melinda C. Power, ScD; Keenan A. Walker, PhD; A. Richey Sharrett, DrPH; Hirofumi Tanaka, PhD; Clifford R. Jack, MD; Thomas H. Mosley, PhD; Robert I. Reid, PhD; Denise A. Reyes, BS; Gerardo Heiss, MD, PhD

***Background*—**Changes in white matter microstructural integrity are detectable before appearance of white matter lesions on magnetic resonance imaging as a manifestation of cerebral small-vessel disease. The information relating poor white matter microstructural integrity to aortic stiffness, a hallmark of aging, is limited. We aimed to examine the association between aortic stiffness and white matter microstructural integrity among older adults.

***Methods and Results*—**We conducted a cross-sectional study to examine the association between aortic stiffness and white matter microstructural integrity among 1484 men and women (mean age, 76 years) at the 2011 to 2013 examination of the ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study). Aortic stiffness was measured as carotid-femoral pulse wave velocity. Cerebral white matter microstructural integrity was measured as fractional anisotropy and mean diffusivity using diffusion tensor imaging. Multivariable linear regression was used to examine the associations of carotid-femoral pulse wave velocity with fractional anisotropy and mean diffusivity of the overall cerebrum and at regions of interest. Each 1-m/s higher carotid-femoral pulse wave velocity was associated with lower overall fractional anisotropy (β=−0.03; 95% CI, −0.05 to −0.02) and higher overall mean diffusivity (β=0.03; 95% CI, 0.02–0.04). High carotid-femoral pulse wave velocity (upper 25th percentile) was associated with lower fractional anisotropy (β=−0.40; 95% CI, −0.61 to −0.20) and higher overall mean diffusivity (β=0.27; 95% CI, 0.10–0.43). Similar associations were observed at individual regions of interest.

***Conclusions*—**High aortic stiffness is associated with low cerebral white matter microstructural integrity among older adults. Aortic stiffness may serve as a target for the prevention of poor cerebral white matter microstructural integrity. **(*J Am Heart Assoc*. 2020;9:e014868. DOI: 10.1161/JAHA.119.014868.)**

Key Words: aortic stiffness • diffusion tensor imaging • white matter integrity

Neurodegenerative conditions have become an increasingly greater burden among older adults. Cerebral small-vessel disease, a set of pathological processes of various causes that affect cerebral small arteries, arterioles, and capillaries, is associated with the risk of dementia.[1,2] White matter around the basal ganglia, the corona radiata, and the subcortical white matter around the ventricles, as well as subcortical nuclei are supplied by deep penetrating arterioles that are susceptible to pathological changes, such as arteriolosclerosis.[3] Structural and functional neuroimaging techniques, including magnetic resonance imaging (MRI), can quantify morphologic changes in the cerebral small vessels.[3]

From the Department of Epidemiology, Gillings School of Global Public Health (J.W., A.K.-N., B.W.P., A.E.A., G.H.), and Department of Emergency Medicine, School of Medicine (M.L.M.), University of North Carolina at Chapel Hill, Chapel Hill, NC; School of Medicine (P.P.) and Department of Epidemiology, Mailman School of Public Health (P.P.), Columbia University, New York, NY; Department of Epidemiology, College of Public Health, University of Kentucky, Lexington, KY (A.K.-N.); Department of Epidemiology and Biostatistics, Milken Institute School of Public Health, Washington, DC (M.C.P.); Department of Neurology, Johns Hopkins University, Baltimore, MD (K.A.W.); Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (A.R.S.); Department of Kinesiology and Health Education, University of Texas at Austin, Austin, TX (H.T.); Departments of Radiology (C.R.J., D.A.R.) and Information Technology (R.I.R.), Mayo Clinic, Rochester, MN; and University of Mississippi Medical Center, Jackson, MS (T.H.M.).

Accompanying Tables S1 through S11 and Figures S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014868

Correspondence to: Jingkai Wei, PhD, Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, 135 Dauer Dr, Chapel Hill, NC 27599. E-mail: jingkai@live.unc.edu

Received October 7, 2019; accepted January 27, 2020.

Clinical Perspective

What Is New?

- Higher levels of aortic stiffness are associated with a lower level of cerebral white matter microstructural integrity, including lower fractional anisotropy and higher mean diffusivity, in a sample of community-dwelling older adults.
- White matter hyperintensity volume partially accounts for the associations between aortic stiffness and lower cerebral white matter microstructural integrity.

What Are the Clinical Implications?

- Future studies are expected to examine the longitudinal association of aortic stiffness with white matter microstructural integrity, as well as the potential opportunity for preservation of white matter microstructural integrity through the lowering of aortic stiffness among older adults.

As detected by MRI, white matter hyperintensities (WMHs) are associated with decreased cognitive performance, particularly executive function.[4]

Microstructural damage to white matter may be found before the detection of WMHs.[5] Although the microstructural pathological features to white matter cannot be captured by conventional MRI,[6] diffusion tensor imaging (DTI) is an MRI tool that quantifies the microstructural integrity of white matter. DTI uses a tensor model to measure both the rate and directionality of the diffusion distributions of water molecules in tissue, which is believed to be an indicator of white matter microstructural integrity, particularly within the axons of neuronal cells.[7] DTI is considered to be sensitive to loss of microstructural integrity in white matter before volumetric MRI is, because demyelination and cell death (as in WMHs) affect diffusion before the cells completely disappear (atrophy).[8,9] WMHs may statistically account for some aspects of white matter microstructural integrity,[10,11] suggesting that DTI measures and WMHs are on a continuum of the same pathological processes.

The elasticity of the aorta facilitates delivery of blood supply to peripheral tissues, dampening sudden oscillations in blood pressure associated with systolic ejection and continuing to promote flow during diastole.[12] Although compliant and elastic during youth, the aorta stiffens with aging as a result of the remodeling of the arterial wall.[13] Increased aortic stiffness, measured as carotid-femoral pulse wave velocity (cfPWV), may lead to insufficient flow wave dampening and a transmission of excessive pulsatile energy into the microvascular bed, particularly in high-flow, low-impendence organs, such as the brain.[14] Increased aortic stiffness has been reported to be associated with cognitive decline and dementia.[12] Like other cardiovascular risk factors, such as hemoglobin A1c, hypertension, and total and low-density lipoprotein cholesterol,[15] cfPWV has been associated with WMH,[16–22] although fewer studies have examined associations of aortic stiffness with white matter microstructural integrity measured with DTI.[18,23–25] Among the latter, the results have been inconsistent, and most studies were based on small study samples. Although results from 2 extant population-based studies suggest that cfPWV is associated with lower fractional anisotropy (FA), an index of white matter microstructural integrity, the associations between cfPWV and mean diffusivity (MD), another important index of white matter microstructural integrity, remain unknown. In addition, the degree to which WMHs account for the associations between cfPWV and DTI measures needs to be further examined. Drawing on the large and well-characterized cohort of European Americans and blacks in the ARIC-NCS (Atherosclerosis Risk in Communities Neurocognitive Study), we aimed to test the hypothesis that higher aortic stiffness is associated with lower white matter microstructural integrity measured by DTI, in a cross-sectional analysis of data from community-dwelling older adults.

Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to Collaborative Studies Coordinating Center at csccmail@unc.edu.

Study Population

During 1987 to 1989, a total of 15 792 men and women, aged 44 to 64 years, were sampled to create a representative cohort of residents of 4 communities in the United States (Forsyth County, North Carolina; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, Maryland).[26] The present study is based on cross-sectional data for ARIC Study cohort members who participated in the fifth examination of this cohort (2011–2013) and had data collected on aortic stiffness (measured as cfPWV) and white matter microstructural integrity (measured with DTI). All participants with evidence of cognitive impairment and a stratified random sample of cognitively normal participants were invited to complete a brain MRI scan (including DTI) as part of ARIC-NCS at visit 5.[27] The ARIC Study protocols were approved by the institutional review boards at each site. All participants provided written informed consent.

To ensure high quality of cfPWV measurements, we excluded from analyses participants with body mass index $\geq$40 kg/m^2 (n=57), participants with evidence of a major arrhythmia on the 12-lead ECG (Minnesota [MN] codes

8-1-3, 8-3-1, and 8-3-2) (n=46), and participants with aortic aneurysm, aortic stenosis, or aortic regurgitation (n=20). No study participant reported peripheral revascularization (assessed as an exclusion criterion). Individuals who self-identified as Asian or American Indian, and as black at the Minnesota or Maryland centers, were excluded because of small numbers (n=12). In addition, we excluded those with prevalent stroke (n=44).

Aortic Stiffness

Aortic stiffness was assessed as cfPWV using the VP-1000 plus system (Omron Co, Ltd, Kyoto, Japan). Participants were required to fast for 8 hours, refrain from smoking, beverages with caffeine, and vigorous physical activity in the morning of the examination day, and bring all prescription and nonprescription medications taken within 2 weeks before the day of the examination visit.[28] The measurement of cfPWV was conducted after participants were supine for approximately 10 minutes.[29] The cfPWV was calculated using the following formula: path length (cm) = [carotid-femoral distance (cm)–(suprasternal notch–carotid distance (cm))]/transit time. Compared with other path length measurements (eg, suprasternal notch-to-femoral distance minus suprasternal notch-to-carotid distance; and carotid-to-femoral distance), this formula shows a similar correlation with cardiovascular events.[30] A minimum of 2 PWV measurements were taken, and the last 2 usable measurements (ie, nonzero values) were averaged. Repeated visits conducted among a subset of participants at each field center approximately 4 to 8 weeks apart (n=79; mean age, 75.7 years; 46 women) yielded an intraclass correlation coefficient and 95% CI for single measurements of 0.70 (0.59–0.81) for cfPWV and approximately 0.82 for averaged cfPWV measurements, according to the Spearman-Brown formula.[28]

Neuroimaging Information

DTI data were measured using 2.7-mm slices for Skyra and Verio scanners and 3-mm slices for Trio scanners.[31] MD (mm^2/s) represents the average rate of diffusion independent of the directionality, and FA (unitless) indicates the fraction of the tensor that can be assigned to anisotropic diffusion.[32,33] Higher MD and lower FA are thought to be independently related to damage in white matter microstructural integrity. Brain regions were defined by Lobar-22 atlas, which is based on the STAND400 template.[34] For each participant, regions of white matter were intersected tissue segmentations from T1-weighted and fluid-attenuated inversion recovery images. Calculation of FA and MD was based on voxels with >50% probability of being white matter, including WMH regions. An upper cutoff of MD <0.002 mm^2/s was applied to exclude edge voxels that were primarily cerebrospinal fluid.[35] We averaged FAs and MDs, separately, across atlas regions and then took a weighted average, with weights based on the number of voxels in each region of white matter, to create white matter FA and MD measures for regions of interest (ROIs), including frontal, temporal, occipital, and parietal lobes, the anterior and posterior corpus callosum, and an overall measure of all ROIs. WMH volume was measured using fluid-attenuated inversion recovery MRI scan and quantified using an algorithm developed at Mayo Clinic, and reported as cm^3.[36]

Covariates

All covariates are based on data collected at visit 1 or visit 5 of the ARIC Study cohort examinations. The covariates were selected for their associations with both aortic stiffness and white matter microstructural integrity, including age (visit 5; years), sex (men/women), race-center (black-Mississippi, black–North Carolina, white–North Carolina, white-Maryland, and white-Minnesota), education (visit 1; below high school; high school/high school equivalent/vocational school; or any college), smoking status (visit 5; ever/never), alcohol drinking status (visit 5; ever/never), body mass index (visit 5; kg/m^2), mean arterial pressure (visit 5; calculated as [1/3*systolic blood pressure]+[2/3*diastolic blood pressure]), diabetes mellitus (visit 5; yes/no; defined as fasting glucose >126 mg/dL, nonfasting glucose >200 mg/dL, self-reported history of diabetes mellitus diagnosis by a physician, or diabetes mellitus medication use), self-reported physical activity (visit 5; total min/wk), heart rate (visit 5; beats per minute), and low-density lipoprotein (visit 5; mmol/dL). In addition, *APOE* genotype (E4 allele ≥1/<1) was also included as a covariate given recent evidence that *APOE4* undermines white matter integrity.[37]

Statistical Analysis

Participant characteristics at visit 5 were analyzed using *t*-test or χ^2 tests by the upper 25th percentile of cfPWV (cfPWV <13.57 m/s). *t*-Tests for FA and MD by categories cfPWV were also conducted. Pearson correlations between FAs and MDs, as well as of cfPWV with FAs and MDs, were estimated.

The ARIC-NCS MRI sampling weights, which were derived to represent all participants at visit 5, were applied in the analysis. Weighted linear regression models were used to assess the associations of cfPWV as a continuous variable with z-scores of DTI measures of overall and regional white matter microstructural integrity (FA and MD). Four sets of analytic models were used. Model 1 was unadjusted; model 2 was adjusted for WMH volumes alone to show to what extent WMH volumes accounted for the unadjusted association

between cfPWV and DTI measures; model 3 was adjusted for all covariates, except WMH volumes (age, sex, race-center, education, *APOE* genotype, smoking status, alcohol drinking status, body mass index, mean arterial pressure, diabetes mellitus, heart rate, and low-density lipoprotein); and model 4 was adjusted for all covariates. The analyses of the associations were stratified by amount of cognitive status (normal or mild cognitive impairment/dementia) and WMH volume (upper 25th percentile of WMH volume or lower 25th percentile of WMH volume). Also, we conducted sensitivity analyses on white matter microstructural integrity of each region with further adjusting for that of other regions.

In addition to the associations of continuous cfPWV with white matter microstructural integrity, we examined the association of elevated cfPWV with white matter microstructural integrity. We implemented a 60% to 40% split of the data set. We used the first data set to define elevated (versus nonelevated) aortic stiffness as the upper 25th percentile, and then used this threshold value to examine the associations of elevated cfPWV with white matter microstructural integrity in the 40% data set.

β Values and 95% CIs were used to summarize associations. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Results

After exclusions, 1484 participants remained in the analytic set (Figure S1). Compared with the ARIC Study visit 5 examinees, our analytic sample had a greater proportion of blacks/study participants from the Jackson, MS, center (28% versus 22%), a smaller proportion of participants from the Minneapolis center (22% versus 31%), a greater proportion of participants with mild cognitive impairment (32.4% versus 19.3%) and dementia (4.3% versus 2.8%), and reported lower levels of leisure-time physical activity (181 versus 192 min/wk) (Table S1). A profile of the participants' characteristics is provided in Table 1. The mean age was 76 years, 40% were men, and 28.6% were black. Compared with participants with cfPWV <13.57 m/s, those with elevated cfPWV were older, more likely to be black, and less likely to have completed high school. In addition, participants with greater cfPWV were less likely to consume alcohol and spent less time engaging in leisure-time physical activities, while being more likely to have diabetes mellitus and higher mean arterial pressure. The WMH volume was, on average, larger among those with elevated, compared with nonelevated, cfPWV.

The FAs of all regions were lower, and MDs of all regions were higher, among participants excluded from analyses, compared with those included (Table S2). The FA and MD values overall and in all ROIs were approximately normally distributed. FA was negatively correlated with MD overall (r=−0.75; P<0.0001) (Table S3). The volume of WMHs was negatively correlated with overall FA (r=−0.45; P<0.0001), and positively correlated with overall MD (r=0.44; P<0.0001). cfPWV was negatively correlated to FAs and positively correlated to MDs (Figure S2).

Aortic Stiffness and FA

The unadjusted linear regression models examining the association of incremental cfPWV with FAs (model 1) indicated that each 1-m/s higher cfPWV was associated with lower FA overall and in all ROIs. When the models were adjusted for all covariates, except WMH volume (model 3), the associations remained statistically significant for overall (β=−0.03; 95% CI, −0.05 to −0.02), and all regions except for anterior corpus callosum (Table 2). The patterns of associations remained for overall as well as frontal lobe, temporal lobe, and parietal lobe after further adjustment for WMH volume (model 4). Stratified by cognitive impairment status (normal versus mild cognitive impairment [MCI] or dementia), cfPWV was associated with lower overall FA and FA at the frontal lobe, temporal lobe, and parietal lobe among participants with normal cognitive function; and associations were present in the posterior corpus callosum, frontal lobe, occipital lobe, and overall FA among participants with mild cognitive impairment or dementia (Table S4). Stratified by quartiles of volume of WMH, cfPWV was associated with lower FAs in the frontal, temporal, occipital, and parietal lobes, as well as overall FA among participants with high volume of WMH (defined as upper 25th percentile). No statistically significant association between cfPWV and FA was observed among participants with low volumes of WMH (defined as the lower 25th percentile) (Table S5). Sensitivity analysis showed that cfPWV was associated with lower FA in temporal lobe after adjustment for FAs of other regions (Table S6).

Aortic Stiffness and MD

The unadjusted linear regression models (model 1) on incremental cfPWV and MDs indicated that each 1-m/s higher cfPWV was associated with higher MD in all ROIs and overall regions. When the models were adjusted for demographic, lifestyle, and clinical covariates (model 3), the associations remained statistically significant for overall measure (β=0.03; 95% CI, 0.02–0.04) and all regions (Table 3). The patterns of associations remained the same with model 3 after further adjustment for WMH volume (model 4). In analyses stratified by cognitive status, cfPWV was associated with higher MDs in overall MD and all regions among participants with normal cognitive function, whereas no association between cfPWV and MD was found among participants with mild cognitive impairment or dementia (Table S7). Once stratified by volume of WMH, cfPWV was associated with higher overall MD and MDs in the frontal, temporal, and occipital lobes among

Table 1. Characteristics of the Study Participants at Visit 5 of the ARIC Study Overall and by the Upper 25th Percentile of cfPWV (n=1484)*

Characteristics	All (n=1484)	Elevated Stiffness (cfPWV ≥13.57 m/s) (n=372)	Nonelevated Stiffness (cfPWV <13.57 m/s) (n=1112)
Age, mean±SD, y	76.1±5.2	78.0±5.2†	75.5±5.1†
Sex, men, n (%)	597 (40.2)	162 (43.6)	435 (39.1)
Race, blacks, n (%)	425 (28.6)	156 (41.9)†	269 (24.2)†
Center, n (%)			
Forsyth County, North Carolina	352 (23.7)	82 (23.3)†	270 (24.3)†
Jackson, MS	403 (27.2)	152 (40.9)†	251 (22.6)†
Minneapolis, MN	327 (22.0)	53 (14.3)†	274 (24.6)†
Washington County, Maryland	402 (27.1)	85 (22.9)†	317 (28.5)†
Education, high school or above, n (%)			
Below high school	198 (13.2)	76 (20.4)†	122 (11.0)†
High school	612 (41.3)	155 (41.7)†	457 (41.2)†
College or above	672 (45.3)	141 (37.9)†	531 (47.9)†
Body mass index, mean±SD, kg/m^2	27.7±4.5	27.5±4.7	27.7±4.4
Ever smoking, n (%)	785 (55.1)	191 (53.5)	594 (55.6)
Ever drinking, n (%)	1119 (76.0)	260 (70.3)†	859 (78.0)†
Mean arterial pressure, mean±SD, mm Hg	87.8±11.4	91.8±11.9†	86.4±10.9†
Hypertension, n (%)	1080 (73.4)	314 (85.1)†	766 (69.5)†
Use of antihypertensive drug, n (%)	1083 (73.0)	303 (81.5)†	780 (70.1)†
Diabetes mellitus, n (%)	392 (26.7)	133 (36.2)†	259 (23.5)†
Heart rate, mean±SD, bpm	64.5±11.0	67.6±11.5†	63.4±10.7†
Total physical activity, mean±SD, min/wk	180.9±176.6	138.3±163.3†	195.3±178.6†
Volume of white matter hyperintensities, mean±SD, cm^3	16.4±16.4	20.9±19.6†	14.9±14.9†
APOE, n (%)			
APOE4 ≥1	1003 (69.9)	254 (70.7)	749 (69.7)
APOE4 <1	431 (30.1)	105 (29.3)	326 (30.3)

ARIC indicates Atherosclerosis Risk in Communities; bpm, beats per minute; cfPWV, carotid-femoral pulse wave velocity.
*The *t*-test was conducted for continuous variables, and the χ^2 test was conducted for categorical variables.
†Statistical significance. Hypertension is defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≤90 mm Hg, and/or self-reported antihypertensive medication use.

participants with high volume of WMH; and associations were found between cfPWV and MDs in the anterior corpus callosum, posterior corpus callosum, and temporal lobe among those with low volume of WMH (defined as lower 25th percentile) (Table S8). Sensitivity analysis showed no significant association between cfPWV and MDs after adjustment for MDs of other regions (Table S9).

Elevated cfPWV and FA

In unadjusted models (model 1) and models adjusted for WMH volumes only (model 2), elevated cfPWV (cfPWV ≥13.65 m/s) compared with nonelevated cfPWV was associated with lower FAs in all ROIs. After adjustment for demographic, lifestyle, and clinical covariates (model 3), the associations remained statistically significant for the overall measure (β=−0.40; 95% CI, −0.61 to −0.20) and all regions (Table S10, Figure—Panel A). The patterns of associations remained statistically significant after further adjusting for WMH volume, except for posterior corpus callosum (model 4).

Elevated cfPWV and MD

Elevated cfPWV was associated with higher MDs in unadjusted models (model 1) for all ROIs. After adjustment for demographic, lifestyle, and clinical covariates (model 3), the associations remained statistically significant for overall measure (β=0.27; 95% CI, 0.10–0.43) and all regions (Table S11, Figure—Panel B). After further adjustment for

Table 2. Associations of cfPWV (per 1-m/s Increment) With FA, Estimated by Linear Regression (n=1484)

	Model 1		Model 2		Model 3		Model 4	
Regions of FA	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Anterior corpus callosum	−0.04 (−0.05 to −0.02)*	<0.0001*	−0.03 (−0.05 to −0.01)*	0.0003*	−0.02 (−0.03 to 0.001)	0.07	−0.01 (−0.03 to 0.003)	0.11
Posterior corpus callosum	−0.03 (−0.04 to −0.01)*	0.001*	−0.02 (−0.03 to −0.001)*	0.04*	−0.02 (−0.04 to −0.002)*	0.03*	−0.02 (−0.03 to 0.002)	0.08
Frontal lobe	−0.06 (−0.07 to −0.04)*	<0.0001*	−0.03 (−0.04 to −0.02)*	<0.0001*	−0.03 (−0.05 to −0.01)*	0.0003*	−0.02 (−0.04 to −0.01)*	0.01
Temporal lobe	−0.03 (−0.05 to −0.01)*	0.0002*	−0.02 (−0.03 to 0.0001)	0.05	−0.04 (−0.06 to −0.02)*	<0.0001*	−0.03 (−0.05 to −0.01)*	0.0003*
Occipital lobe	−0.03 (−0.05 to −0.01)*	0.001*	−0.02 (−0.04 to −0.003)*	0.02*	−0.02 (−0.04 to −0.004)*	0.02*	−0.02 (−0.04 to 0.0001)	0.05
Parietal lobe	−0.04 (−0.06 to −0.02)*	<0.0001*	−0.01 (−0.03 to 0.002)	0.08	−0.03 (−0.04 to −0.01)*	0.002*	−0.02 (−0.03 to −0.001)*	0.03*
Overall	−0.05 (−0.07 to −0.03)*	<0.0001*	−0.03 (−0.04 to −0.01)*	0.001*	−0.03 (−0.05 to −0.02)*	0.0001*	−0.02 (−0.04 to −0.01)*	0.002*

Model 1, unadjusted. Model 2, adjusted for volume of white matter hyperintensities. Model 3, adjusted for age, sex, race-center, education, *APOE* genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes mellitus, physical activity (total min/wk), low-density lipoprotein cholesterol, and heart rate. Model 4, adjusted for factors included in model 2 and model 3. cfPWV indicates carotid-femoral pulse wave velocity; FA, fractional anisotropy.
*Statistical significance. The β is the difference (unadjusted for model 1 and adjusted for model 2 to model 4) of FA values for each 1-m/s cfPWV increment.

WMH volume (model 4), except for temporal lobe and occipital lobe, all the associations remained.

Discussion

In this cross-sectional analysis of a sample of community-dwelling older white and black adults in the United States, we found an association of greater aortic stiffness with lower cerebral white matter microstructural integrity (ie, lower FAs and high MDs) overall and in different regions of the cerebrum. The associations were independent of potential confounders, including education and other demographic factors, lifestyle factors, and phenotypes related to vascular diseases (ie, hypertension and diabetes mellitus). WMH

Table 3. Associations of cfPWV (per 1-m/s Increment) With MD, Estimated by Linear Regression (n=1484)

	Model 1		Model 2		Model 3		Model 4	
Regions of MD	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value	β (95% CI)	*P* Value
Anterior corpus callosum	0.04 (0.03 to 0.06)*	<0.0001*	0.04 (0.02 to 0.05)*	<0.0001*	0.02 (0.01 to 0.04)*	0.002*	0.02 (0.01 to 0.04)*	0.003*
Posterior corpus callosum	0.02 (0.003 to 0.04)*	0.02*	0.01 (−0.003 to 0.03)	0.10	0.02 (0.01 to 0.04)*	0.003*	0.02 (0.01 to 0.04)*	0.01*
Frontal lobe	0.06 (0.04 to 0.07)*	<0.0001*	0.03 (0.02 to 0.04)*	<0.0001*	0.03 (0.02 to 0.05)*	<0.0001*	0.02 (0.01 to 0.04)*	0.001
Temporal lobe	0.05 (0.03 to 0.06)*	<0.0001*	0.03 (0.01 to 0.04)*	0.0003*	0.03 (0.02 to 0.04)*	<0.0001*	0.02 (0.01 to 0.04)*	0.0004*
Occipital lobe	0.04 (0.03 to 0.06)*	<0.0001*	0.03 (0.02 to 0.05)*	<0.0001*	0.02 (0.01 to 0.04)*	0.01*	0.02 (0.001 to 0.03)*	0.03*
Parietal lobe	0.04 (0.03 to 0.06)*	<0.0001*	0.02 (0.003 to 0.03)*	0.02*	0.03 (0.01 to 0.04)*	0.001*	0.02 (0.004 to 0.03)*	0.01*
Overall	0.05 (0.04 to 0.07)*	<0.0001*	0.03 (0.01 to 0.04)*	0.0001*	0.03 (0.02 to 0.04)*	<0.0001*	0.02 (0.01 to 0.03)*	0.001*

Model 1, unadjusted. Model 2, adjusted for volume of white matter hyperintensities. Model 3, adjusted for age, sex, race-center, education, *APOE* genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes mellitus, physical activity (total min/wk), low-density lipoprotein cholesterol, and heart rate. Model 4, adjusted for factors included in model 2 and model 3. cfPWV indicates carotid-femoral pulse wave velocity; MD, mean diffusivity.
*Statistical significance. The β is the difference (unadjusted for model 1 and adjusted for model 2 to model 4) of MD values for each 1-m/s cfPWV increment.

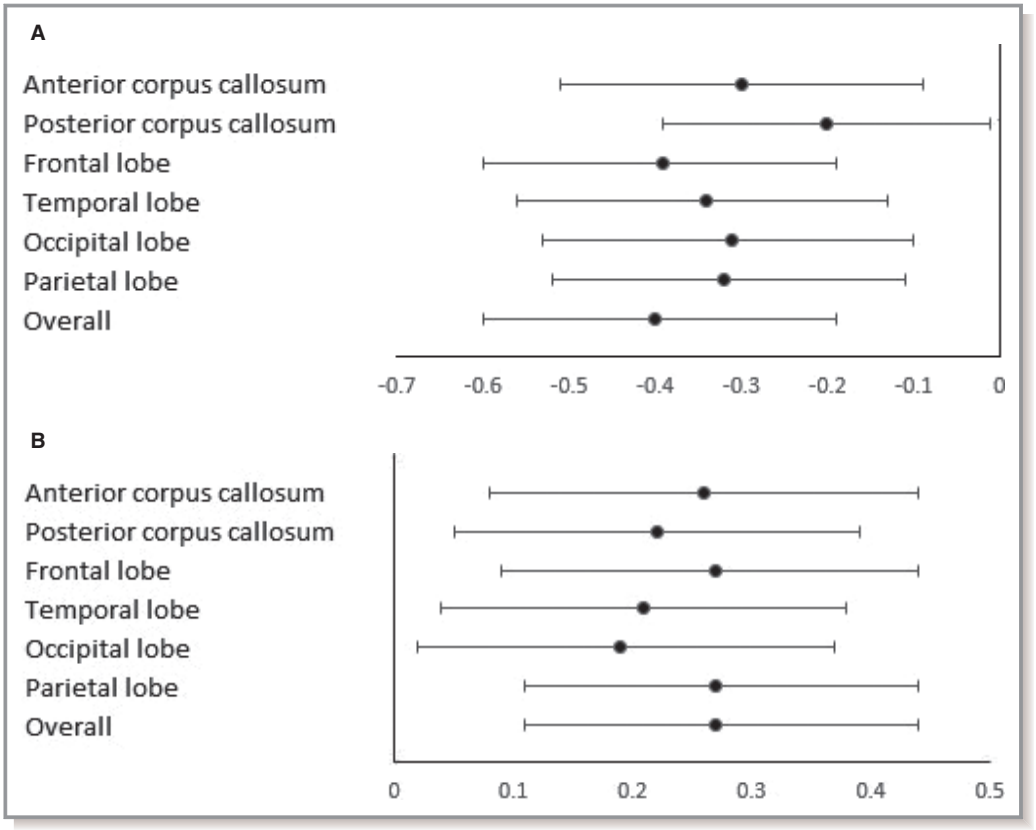


Figure. The adjusted difference of fractional anisotropy (**A**) and mean diffusivity (**B**) by high and nonhigh carotid-femoral pulse wave velocity for overall brain region and specific regions of interest (figures were based on model 3).

volume partially accounts for the associations between aortic stiffness and lower cerebral white matter microstructural integrity, but associations remain after adjusting for WMH volume.

The results of our cross-sectional study are consistent with prior cross-sectional studies,[23–25] although the effect sizes of associations in our study were smaller, which may be because of younger age of participants with lower aortic stiffness in the prior studies. However, evidence from population-based studies is sparse. Our results agree with those of Maillard et al,[38] who reported higher cfPWV to be associated with lower regional FA in a study of a young cohort composed of mostly white participants. In the Health ABC (Health, Aging and Body Composition) Study of 303 older adults (mean age, 82.9 years; 41% black), Rosano et al[18] reported that high cfPWV was correlated with low total cerebral FA, although the association was not statistically supported after adjustment for total WMH. These findings differ from what we reported in our study. We attribute these disparate results to differences in study design, as well as different methods of measurement for cfPWV. The Health ABC Study was a cross-temporal analysis of cfPWV measured 10 years before the assessment of white matter lesions in association with white matter structural integrity. Although this study supports a temporal association between cfPWV and loss of white matter structural integrity, it does not directly assess how past aortic stiffness may be associated with later white matter integrity.

Hemodynamic factors likely play a role in the association between aortic stiffness and cerebral white matter integrity. The age-related process of aortic stiffening increases pulsatility, facilitating transmission of excessive pulse pressure into the cerebral circulation. This may trigger microvascular changes that limit flow, leading to ischemia and neural damage.[14,21]

Our results show that volume of WMHs partially accounts for the associations between aortic stiffness and cerebral white matter microstructural integrity, which is consistent with previous findings that macrostructural and microstructural cerebral white matter degeneration reflect the same underlying pathophysiological changes.[39] Also, our study has shown that the associations between aortic stiffness and white matter microstructural integrity were stronger among participants with higher WMH volume, which suggests cfPWV may be a better indicator of poorer white matter microstructural integrity with poorer macrostructural integrity.

Our study showed that the associations between cfPWV and white matter microstructural integrity were stronger among participants with normal cognitive function, particularly for MDs, although this may be because of a larger sample size of those with normal cognition. The associations of aortic stiffness with white matter microstructural integrity by cognitive status deserve further investigation.

Our study has public health relevance. Because DTI appears to detect white matter changes in an earlier stage than what can be observed through traditional MRI, FA and MD may be better indexes of the impact of hemodynamic changes on the brain, facilitating early detection of pathological changes in white matter. Future research should also consider the potential for cfPWV as an important risk factor for loss of cerebral white matter microstructural integrity, with its downstream manifestations of cognitive decline and dementia. On the basis of our analytic sample, each 1-m/s increment in cfPWV was associated with a decrease in cerebral white matter microstructural integrity in a linear manner, suggesting the absence of thresholds below which cfPWV is not associated with lower white matter integrity. Given these results, replication in longitudinal studies of aortic stiffness and change of white matter microstructural integrity is needed. If confirmed, cfPWV should be considered as an intervention target for opportunities to reduce aortic stiffness across the range of the measurement, not only among those with high cfPWV. Several studies have shown that aortic stiffness can be reduced via pharmacologic agents[40,41] and nonpharmacological interventions.[42–44] In addition, given the smaller effect sizes of the associations in our study, compared with those reported by previous studies based on data for young adults, efforts to reduce aortic stiffness may be most beneficial for brain health well before older adulthood, such as during midlife.

Our study has several strengths. The study's large, population-based number of examinees facilitates generalizability to community-dwelling older adults. Furthermore, data collection was based on standardized protocols administered by trained personnel, and used validated measurements for aortic stiffness, as well as white matter microstructural and macrostructural integrity.

The main limitation of our study is its cross-sectional design, which limits causal inferences about the association of aortic stiffness with cerebral white matter microstructural integrity among older adults; and possibilities that participants with white matter related disease (eg, depression) may affect cfPWV with poor lifestyle cannot be excluded. Moreover, all participants in this study had some degree of WMH, preventing the study of associations between cfPWV and DTI measures in the absence of WMH. However, our sensitivity analysis identified the difference in associations at high and low WMH volumes. Last, this study is restricted to older adults who were survivors from the start of the ARIC Study, subject to selection bias.

Conclusions

In conclusion, higher aortic stiffness is associated with lower cerebral white matter microstructural integrity among older adults. Future research should examine the longitudinal association of aortic stiffness with white matter microstructural integrity, as well as the potential opportunity for preservation of white matter microstructural integrity through the lowering of aortic stiffness.

Acknowledgments

The authors thank the staff and participants of the ARIC (Atherosclerosis Risk in Communities) Study for their important contributions.

Sources of Funding

The ARIC (Atherosclerosis Risk in Communities) Study is performed as a collaborative study supported by National Heart, Lung, and Blood Institute (NHLBI) contracts (HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, and HHSN268201700004I). Support for the pulse wave velocity component was provided by R01AG053938. The imaging data were collected by U012U01HL096812, 2U01HL096814, 2U01HL096899, 2U01HL096902, and 2U01HL096917 from the National Institutes of Health (NHLBI, National Institute of Neurological Disorders and Stroke, National Institute on Aging [NIA], and National Institute on Deafness and Other Communication Disorders), and with previous brain magnetic resonance imaging examinations funded by R01-HL70825 from the NHLBI. Dr Palta is supported by grant K99AG052830 from the NIA.

Disclosures

None.

References

1. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol*. 2013;12:483–497.
2. Bos D, Wolters FJ, Darweesh SKL, Vernooij MW, de Wolf F, Ikram MA, Hofman A. Cerebral small vessel disease and the risk of dementia: a systematic review and meta-analysis of population-based evidence. *Alzheimers Dement*. 2018;14:1482–1492.
3. Pasi M, van Uden IW, Tuladhar AM, de Leeuw FE, Pantoni L. White matter microstructural damage on diffusion tensor imaging in cerebral small vessel disease: clinical consequences. *Stroke*. 2016;47:1679–1684.
4. Oosterman JM, Sergeant JA, Weinstein HC, Scherder EJ. Timed executive functions and white matter in aging with and without cardiovascular risk factors. *Rev Neurosci*. 2004;15:439–462.

5. Maillard P, Fletcher E, Harvey D, Carmichael O, Reed B, Mungas D, DeCarli C. White matter hyperintensity penumbra. *Stroke*. 2011;42:1917–1922.
6. O'Sullivan M, Morris RG, Huckstep B, Jones DK, Williams SC, Markus HS. Diffusion tensor MRI correlates with executive dysfunction in patients with ischaemic leukoaraiosis. *J Neurol Neurosurg Psychiatry*. 2004;75:441–447.
7. Madden DJ, Bennett IJ, Song AW. Cerebral white matter integrity and cognitive aging: contributions from diffusion tensor imaging. *Neuropsychol Rev*. 2009;19:415–435.
8. Maniega SM, Valdes Hernandez MC, Clayden JD, Royle NA, Murray C, Morris Z, Aribisala BS, Gow AJ, Starr JM, Bastin ME, Deary IJ, Wardlaw JM. White matter hyperintensities and normal-appearing white matter integrity in the aging brain. *Neurobiol Aging*. 2015;36:909–918.
9. Maillard P, Fletcher E, Lockhart SN, Roach AE, Reed B, Mungas D, DeCarli C, Carmichael OT. White matter hyperintensities and their penumbra lie along a continuum of injury in the aging brain. *Stroke*. 2014;45:1721–1726.
10. Vernooij MW, de Groot M, van der Lugt A, Ikram MA, Krestin GP, Hofman A, Niessen WJ, Breteler MM. White matter atrophy and lesion formation explain the loss of structural integrity of white matter in aging. *NeuroImage*. 2008;43:470–477.
11. de Groot M, Ikram MA, Akoudad S, Krestin GP, Hofman A, van der Lugt A, Niessen WJ, Vernooij MW. Tract-specific white matter degeneration in aging: the Rotterdam study. *Alzheimers Dement*. 2015;11:321–330.
12. Sethi S, Rivera O, Oliveros R, Chilton R. Aortic stiffness: pathophysiology, clinical implications, and approach to treatment. *Integr Blood Press Control*. 2014;7:29–34.
13. Kucharska-Newton AM, Stoner L, Meyer ML. Determinants of vascular age: an epidemiological perspective. *Clin Chem*. 2019;65:108–118.
14. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility–Reykjavik study. *Brain*. 2011;134:3398–3407.
15. Murray AD, Staff RT, Shenkin SD, Deary IJ, Starr JM, Whalley LJ. Brain white matter hyperintensities: relative importance of vascular risk factors in nondemented elderly people. *Radiology*. 2005;237:251–257.
16. van Sloten TT, Protogerou AD, Henry RM, Schram MT, Launer LJ, Stehouwer CD. Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2015;53:121–130.
17. King KS, Chen KX, Hulsey KM, McColl RW, Weiner MF, Nakonezny PA, Peshock RM. White matter hyperintensities: use of aortic arch pulse wave velocity to predict volume independent of other cardiovascular risk factors. *Radiology*. 2013;267:709–717.
18. Rosano C, Watson N, Chang Y, Newman AB, Aizenstein HJ, Du Y, Venkatraman V, Harris TB, Barinas-Mitchell E, Sutton-Tyrrell K. Aortic pulse wave velocity predicts focal white matter hyperintensities in a biracial cohort of older adults. *Hypertension*. 2013;61:160–165.
19. Tap L, van Opbroek A, Niessen WJ, Smits M, Mattace-Raso FU. Aortic stiffness and brain integrity in elderly patients with cognitive and functional complaints. *Clin Interv Aging*. 2018;13:2161–2167.
20. Gustavsson AM, Stomrud E, Abul-Kasim K, Minthon L, Nilsson PM, Hansson O, Nagga K. Cerebral microbleeds and white matter hyperintensities in cognitively healthy elderly: a cross-sectional cohort study evaluating the effect of arterial stiffness. *Cerebrovasc Dis Extra*. 2015;5:41–51.
21. Palta P, Sharrett AR, Wei J, Meyer ML, Kucharska-Newton A, Power MC, Deal JA, Jack CR, Knopman D, Wright J, Griswold M, Tanaka H, Mosley TH, Heiss G. Central arterial stiffness is associated with structural brain damage and poorer cognitive performance: the ARIC study. *J Am Heart Assoc*. 2019;8:e011045. 10.1161/JAHA.118.011045.
22. Henskens LH, Kroon AA, van Oostenbrugge RJ, Gronenschild EH, Fuss-Lejeune MM, Hofman PA, Lodder J, de Leeuw PW. Increased aortic pulse wave velocity is associated with silent cerebral small-vessel disease in hypertensive patients. *Hypertension*. 2008;52:1120–1126.
23. Tarumi T, de Jong DL, Zhu DC, Tseng BY, Liu J, Hill C, Riley J, Womack KB, Kerwin DR, Lu H, Munro Cullum C, Zhang R. Central artery stiffness, baroreflex sensitivity, and brain white matter neuronal fiber integrity in older adults. *NeuroImage*. 2015;110:162–170.
24. Sala M, van den Berg-Huysmans A, van der Grond J, Huisman M, Brandts A, Westenberg JJ, de Roos A. Aortic arch stiffness is associated with incipient brain injury in patients with hypertension. *Am J Hypertens*. 2016;29:705–712.
25. Tjeerdema N, Van Schinkel LD, Westenberg JJ, Van Elderen SG, Van Buchem MA, Smit JW, Van der Grond J, De Roos A. Aortic stiffness is associated with white matter integrity in patients with type 1 diabetes. *Eur Radiol*. 2014;24:2031–2037.
26. The ARIC investigators. The atherosclerosis risk in communities (ARIC) study: design and objectives. *Am J Epidemiol*. 1989;129:687–702.
27. Knopman DS, Griswold ME, Lirette ST, Gottesman RF, Kantarci K, Sharrett AR, Jack CR Jr, Graff-Radford J, Schneider AL, Windham BG, Coker LH, Albert MS, Mosley TH Jr. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. *Stroke*. 2015;46:433–440.
28. Meyer ML, Tanaka H, Palta P, Patel MD, Camplain R, Couper D, Cheng S, Al Qunaibet A, Poon AK, Heiss G. Repeatability of central and peripheral pulse wave velocity measures: the atherosclerosis risk in communities (ARIC) study. *Am J Hypertens*. 2016;29:470–475.
29. Meyer ML, Tanaka H, Palta P, Cheng S, Gouskova N, Aguilar D, Heiss G. Correlates of segmental pulse wave velocity in older adults: the atherosclerosis risk in communities (ARIC) study. *Am J Hypertens*. 2016;29:114–122.
30. Nemeth ZK, Studinger P, Kiss I, Othmane Tel H, Nemcsik J, Fekete BC, Deak G, Egresits J, Szathmari M, Tisler A. The method of distance measurement and torso length influences the relationship of pulse wave velocity to cardiovascular mortality. *Am J Hypertens*. 2011;24:155–161.
31. Schneider ALC, Selvin E, Sharrett AR, Griswold M, Coresh J, Jack CR, Knopman D, Mosley T, Gottesman RF. Diabetes, prediabetes, and brain volumes and subclinical cerebrovascular disease on MRI: the atherosclerosis risk in communities neurocognitive study (ARIC-NCS). *Diabetes Care*. 2017;40:1514.
32. Madden DJ, Bennett IJ, Burzynska A, Potter GG, Chen NK, Song AW. Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochem Biophys Acta*. 2012;1822:386–400.
33. Power MC, Tingle JV, Reid RI, Huang J, Sharrett AR, Coresh J, Griswold M, Kantarci K, Jack CR Jr, Knopman D, Gottesman RF, Mosley TH. Midlife and late-life vascular risk factors and white matter microstructural integrity: the atherosclerosis risk in communities neurocognitive study. *J Am Heart Assoc*. 2017;6:e005608. DOI: 10.1161/JAHA.117.005608.
34. Vemuri P, Gunter JL, Senjem ML, Whitwell JL, Kantarci K, Knopman DS, Boeve BF, Petersen RC, Jack CR Jr. Alzheimer's disease diagnosis in individual subjects using structural MR images: validation studies. *NeuroImage*. 2008;39:1186–1197.
35. Walker KA, Power MC, Hoogeveen RC, Folsom AR, Ballantyne CM, Knopman DS, Windham BG, Selvin E, Jack CR Jr, Gottesman RF. Midlife systemic inflammation, late-life white matter integrity, and cerebral small vessel disease: the atherosclerosis risk in communities study. *Stroke*. 2017;48:3196–3202.
36. Raz L, Jayachandran M, Tosakulwong N, Lesnick TG, Wille SM, Murphy MC, Senjem ML, Gunter JL, Vemuri P, Jack CR Jr, Miller VM, Kantarci K. Thrombogenic microvesicles and white matter hyperintensities in postmenopausal women. *Neurology*. 2013;80:911–918.
37. Koizumi K, Hattori Y, Ahn SJ, Buendia I, Ciacciarelli A, Uekawa K, Wang G, Hiller A, Zhao L, Voss HU, Paul SM, Schaffer C, Park L, Iadecola C. Apoε4 disrupts neurovascular regulation and undermines white matter integrity and cognitive function. *Nat Commun*. 2018;9:3816.
38. Maillard P, Mitchell GF, Himali JJ, Beiser A, Fletcher E, Tsao CW, Pase MP, Satizabal CL, Vasan RS, Seshadri S, DeCarli C. Aortic stiffness, increased white matter free water, and altered microstructural integrity: a continuum of injury. *Stroke*. 2017;48:1567–1573.
39. Pelletier A, Periot O, Dilharreguy B, Hiba B, Bordessoules M, Chanraud S, Peres K, Amieva H, Dartigues JF, Allard M, Catheline G. Age-related modifications of diffusion tensor imaging parameters and white matter hyperintensities as inter-dependent processes. *Front Aging Neurosci*. 2015;7:255.
40. Chen X, Huang B, Liu M, Li X. Effects of different types of antihypertensive agents on arterial stiffness: a systematic review and meta-analysis of randomized controlled trials. *J Thorac Dis*. 2015;7:2339–2347.
41. Upala S, Wirunsawanya K, Jaruvongvanich V, Sanguankeo A. Effects of statin therapy on arterial stiffness: a systematic review and meta-analysis of randomized controlled trial. *Int J Cardiol*. 2017;227:338–341.
42. Ashor AW, Lara J, Siervo M, Celis-Morales C, Mathers JC. Effects of exercise modalities on arterial stiffness and wave reflection: a systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2014;9:e110034.
43. Nordstrand N, Gjevestad E, Hertel JK, Johnson LK, Saltvedt E, Roislien J, Hjelmesaeth J. Arterial stiffness, lifestyle intervention and a low-calorie diet in morbidly obese patients-a nonrandomized clinical trial. *Obesity (Silver Spring)*. 2013;21:690–697.
44. Jatoi NA, Jerrard-Dunne P, Feely J, Mahmud A. Impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. *Hypertension*. 2007;49:981–985.

Supplemental Material

Table S1. Characteristics of participants included in the analysis and the whole sample with cfPWV at visit 5.

	Participants included in the study (n=1,484)	All visit 5 participants with inclusion criteria* (n=4,539)
Age, year, mean ± SD	76.1±5.2	75.2±5.0
Sex, men, n (%)	597 (40.2)	1,832 (40.4)
Race, African Americans, n (%)	425 (28.6)	984 (21.7)
Center, n (%)		
Forsyth, NC	352 (23.7)	943 (20.8)
Jackson, MS	403 (27.2)	925 (20.4)
Minneapolis, MN	327 (22.0)	1,388 (30.6)
Washington, MD	402 (27.1)	1,283 (28.3)
Education, high school or above, n (%)		
Below high school	198 (13.2)	574 (12.7)
High school	612 (41.3)	1,911 (42.2)
College or above	672 (45.3)	2,047 (45.2)
Body mass index, kg/m^2, mean ± SD	27.7±4.5	27.8±4.5
Ever smoking, n (%)	785 (55.1)	2,402 (55.6)
Ever drinking, n (%)	1,119 (76.0)	3,535 (78.8)
Mean arterial pressure, mmHg, mean ± SD	87.8±11.4	87.5±11.3
Hypertension, n (%)	1,080 (73.4)	3,239 (72.1)
Use of antihypertensive drug, n (%)	1,083 (73.0)	3,262 (72.0)
Diabetes, n (%)	392 (26.7)	1,135 (25.2)
Heart rate, bpm, mean ± SD	64.5±11.0	64.7±10.9
Carotid-femoral pulse wave velocity, m/s	11.8±3.3	11.6±3.1
Total physical activity, minutes/week, mean ± SD	180.9±176.6	192.5±187.6
APOE, n (%)		
APOE4 ≥1	1,003 (69.9)	3,119 (71.4)
APOE4 <1	431 (30.1)	1,247 (28.6)
Cognitive status, n (%)		
Normal	937 (63.1)	3514 (77.7)
Mild cognitive impairment	481 (32.4)	872 (19.3)
Dementia	64 (4.3)	128 (2.8)

*This applies to all inclusion criteria based on cfPWV

Table S2. Mean fractional anisotropy (FA) and mean diffusivity (MD) among included and excluded participants. ARIC study examination visit 5.

	FA			MD (10^{-4} mm^2/s)		
Regions	Excluded (n=458)	Included (n=1,484)	Difference (SE)	Excluded (n=458)	Included (n=1,484)	Difference (SE)
Anterior corpus callosum	**0.407±0.06**	**0.424±0.06**	**-0.017 (0.003)**	**11.9±1.2**	**11.6±1.1**	**0.3 (0.06)**
Posterior corpus callosum	**0.559±0.07**	**0.578±0.06**	**-0.019 (0.003)**	**11.4±1.1**	**11.1±1.0**	**0.3 (0.06)**
Frontal lobe	**0.271±0.02**	**0.280±0.02**	**-0.009 (0.001)**	**8.8±0.6**	**8.6±0.5**	**0.3 (0.03)**
Temporal lobe	**0.275±0.02**	**0.283±0.02**	**-0.008 (0.001)**	**9.0±0.7**	**8.8±0.5**	**0.3 (0.03)**
Occipital lobe	**0.223±0.03**	**0.229±0.02**	**-0.007 (0.001)**	**9.0±0.7**	**8.8±0.6**	**0.2 (0.03)**
Parietal lobe	**0.290±0.03**	**0.300±0.02**	**-0.010 (0.001)**	**9.0±0.7**	**8.7±0.6**	**0.3 (0.03)**
Overall	**0.275±0.02**	**0.284±0.02**	**-0.009 (0.001)**	**9.0±0.6**	**8.7±0.5**	**0.3 (0.03)**

T-test was conducted for FAs and MDs listed above. Bold indicates at $p<0.05$ from a t-test.

Table S3. Correlations between FA and MD at different regions.

Regions	Correlation	P value
Frontal lobe	-0.75	<0.0001
Temporal lobe	-0.63	<0.0001
Occipital lobe	-0.68	<0.0001
Parietal lobe	-0.67	<0.0001
Anterior corpus callosum	-0.50	<0.0001
Posterior corpus callosum	-0.66	<0.0001
Overall	-0.75	<0.0001

ARIC study examination visit 5.

Table S4. Association of cfPWV and z-scores of FA. Mean differences estimated by multivariable linear regression by cognitive status.

Regions	Cognitive status	cfPWV (m/s)							
		Model 1 β (95% CI)	P value	Model 2 β (95% CI)	P value	Model 3 β (95% CI)	P value	Model 4 β (95% CI)	P value
Anterior corpus callosum	Normal (n=937)	**-0.04 (-0.06, -0.01)**	**0.001**	**-0.03 (-0.05, -0.01)**	**0.01**	-0.01 (-0.04, 0.01)	0.30	-0.01 (-0.03, 0.01)	0.37
	MCI/dementia (n=545)	**-0.03 (-0.05, -0.004)**	**0.02**	-0.02 (-0.05, 0.003)	0.08	-0.03 (-0.06, 0.001)	0.06	-0.03 (-0.05, 0.002)	0.07
Posterior corpus callosum	Normal (n=937)	**-0.02 (-0.04, -0.001)**	**0.04**	-0.01 (-0.03, 0.01)	0.19	-0.02 (-0.04, 0.005)	0.13	-0.01 (-0.03, 0.01)	0.22
	MCI/dementia (n=545)	**-0.03 (-0.06, -0.003)**	**0.03**	-0.02 (-0.04, 0.01)	0.23	**-0.03 (-0.06, -0.0001)**	**0.05**	-0.03 (-0.06, 0.001)	0.06
Frontal lobe	Normal (n=937)	**-0.06 (-0.08, -0.04)**	**<0.0001**	**-0.03 (-0.05, -0.01)**	**0.002**	**-0.03 (-0.05, -0.01)**	**0.01**	**-0.02 (-0.04, -0.0001)**	**0.05**
	MCI/dementia (n=545)	**-0.05 (-0.08, -0.03)**	**<0.0001**	**-0.03 (-0.05, -0.01)**	**0.01**	**-0.03 (-0.05, -0.0000)**	**0.05**	**-0.02 (-0.05, -0.0004)**	**0.05**
Temporal lobe	Normal (n=937)	**-0.03 (-0.05, -0.01)**	**0.002**	-0.02 (-0.04, 0.003)	0.09	**-0.04 (-0.06, -0.02)**	**0.0003**	**-0.03 (-0.06, -0.01)**	**0.002**
	MCI/dementia (n=545)	-0.02 (-0.04, 0.01)	0.17	-0.01 (-0.03, 0.02)	0.56	-0.02 (-0.05, 0.01)	0.22	-0.02 (-0.05, 0.01)	0.25
Occipital lobe	Normal (n=936)	**-0.03 (-0.05, -0.004)**	**0.02**	-0.02 (-0.04, 0.01)	0.16	-0.02 (-0.04, 0.01)	0.17	-0.01 (-0.04, 0.01)	0.30
	MCI/dementia (n=545)	**-0.03 (-0.06, -0.01)**	**0.004**	**-0.03 (-0.05, -0.004)**	**0.02**	**-0.03 (-0.05, -0.001)**	**0.04**	**-0.03 (-0.05, -0.001)**	**0.05**
Parietal lobe	Normal (n=937)	**-0.04 (-0.06, -0.02)**	**0.0003**	-0.01 (-0.03, 0.01)	0.24	**-0.03 (-0.05, -0.004)**	**0.02**	-0.01 (-0.03, 0.005)	0.15
	MCI/dementia (n=545)	**-0.04 (-0.07, -0.02)**	**0.002**	-0.02 (-0.04, 0.003)	0.09	-0.02 (-0.05, 0.01)	0.11	-0.02 (-0.04, 0.005)	0.12
Overall	Normal (n=936)	**-0.05 (-0.07, -0.03)**	**<0.0001**	**-0.03 (-0.04, -0.01)**	**0.01**	**-0.03 (-0.05, -0.01)**	**0.003**	**-0.02 (-0.04, -0.003)**	**0.03**
	MCI/dementia (n=545)	**-0.05 (-0.07, -0.02)**	**0.0003**	**-0.03 (-0.05, -0.004)**	**0.02**	**-0.03 (-0.06, -0.001)**	**0.04**	**-0.03 (-0.05, -0.001)**	**0.04**

Bold indicates statistical significance. β is the difference (unadjusted for Model 1, adjusted for Model 2 to Model 4) of MDs between high and non-high cfPWV.

Model 1: Unadjusted.

Model 2: Adjusted for volume of white matter hyperintensities.

Model 3: Adjusted for age, sex, race-center, education, APOE genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes, physical activity (total minutes/week), LDL-C, heart rate

Model 4: Adjusted for factors included in Model 2 and Model 3.

Table S6. Association of cfPWV and z-scores of FA (n=1484). Mean differences estimated by multivariable linear regression by WMH volumes.

Regions	Cognitive status	cfPWV (m/s)							
		Model 1 β (95% CI)	P value	Model 2 β (95% CI)	P value	Model 3 β (95% CI)	P value	Model 4 β (95% CI)	P value
Anterior corpus callosum	High WMH volume (n=371)	**-0.03 (-0.06, -0.003)**	**0.03**	-0.03 (-0.06, 0.001)	0.05	-0.01 (-0.05, 0.02)	0.40	-0.01 (-0.05, 0.02)	0.47
	Low WMH volume (n=371)	-0.03 (-0.06, 0.01)	0.13	-0.03 (-0.07, 0.01)	0.13	-0.03 (-0.07, 0.01)	0.10	-0.03 (-0.07, 0.01)	0.09
Posterior corpus callosum	High WMH volume (n=371)	**-0.03 (-0.06, -0.002)**	**0.03**	-0.02 (-0.05, 0.01)	0.13	-0.01 (-0.04, 0.03)	0.61	-0.003 (-0.04, 0.03)	0.88
	Low WMH volume (n=371)	-0.002 (-0.04, 0.03)	0.91	0.00004 (-0.03, 0.03)	0.99	-0.03 (-0.07, 0.01)	0.12	-0.03 (-0.06, 0.01)	0.15
Frontal lobe	High WMH volume (n=371)	**-0.07 (-0.10, -0.04)**	**<0.0001**	**-0.05 (-0.07, -0.02)**	**0.001**	**-0.05 (-0.09, -0.02)**	**0.001**	**-0.04 (-0.07, -0.02)**	**0.002**
	Low WMH volume (n=371)	-0.02 (-0.06, 0.01)	0.14	-0.02 (-0.05, 0.01)	0.27	-0.02 (-0.06, 0.01)	0.15	-0.02 (-0.06, 0.01)	0.17
Temporal lobe	High WMH volume (n=371)	**-0.05 (-0.08, -0.01)**	**0.004**	**-0.03 (-0.06, -0.002)**	**0.04**	**-0.05 (-0.08, -0.02)**	**0.002**	**-0.04 (-0.08, -0.01)**	**0.01**
	Low WMH volume (n=371)	-0.02 (-0.05, 0.02)	0.35	-0.02 (-0.05, 0.02)	0.37	-0.03 (-0.07, 0.005)	0.09	-0.03 (-0.07, 0.004)	0.07
Occipital lobe	High WMH volume (n=371)	**-0.06 (-0.09, -0.03)**	**0.0001**	**-0.05 (-0.08, -0.02)**	**0.001**	**-0.05 (-0.08, -0.02)**	**0.003**	**-0.04 (-0.08, -0.01)**	**0.01**
	Low WMH volume (n=371)	0.002 (-0.03, 0.04)	0.90	0.005 (-0.03, 0.04)	0.80	0.003 (-0.04, 0.04)	**0.04**	0.003 (-0.04, 0.04)	0.90
Parietal lobe	High WMH volume (n=371)	**-0.06 (-0.09, -0.03)**	**0.0003**	**-0.03 (-0.06, -0.01)**	**0.02**	**-0.04 (-0.08, -0.01)**	**0.01**	**-0.03 (-0.06, -0.001)**	**0.04**
	Low WMH volume (n=371)	-0.01 (-0.04, 0.02)	0.64	-0.002 (-0.03, 0.03)	0.89	-0.01 (-0.04, 0.02)	0.49	-0.01 (-0.04, 0.02)	0.54
Overall	High WMH volume (n=371)	**-0.07 (-0.10, -0.04)**	**<0.0001**	**-0.05 (-0.07, -0.02)**	**0.001**	**-0.06 (-0.09, -0.02)**	**0.001**	**-0.04 (-0.07, -0.02)**	**0.003**
	Low WMH volume (n=371)	-0.02 (-0.05, 0.01)	0.27	-0.01 (-0.05, 0.02)	0.42	-0.02 (-0.06, 0.01)	0.19	-0.02 (-0.06, 0.01)	0.21

Bold indicates statistical significance. β is the difference (unadjusted for Model 1, adjusted for Model 2 to Model 4) of MDs between high and non-high cfPWV.

Model 1: Unadjusted.

Model 2: Adjusted for volume of white matter hyperintensities.

Model 3: Adjusted for age, sex, race-center, education, APOE genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes, physical activity (total minutes/week), LDL-C, heart rate

Model 4: Adjusted for factors included in Model 2 and Model 3.

Table S8. Association of cfPWV and z-scores of FA (n=1484). Mean differences estimated by multivariable linear regression with further adjustment for FAs of other locations.

Regions	cfPWV (m/s)							
	Model 1 β (95% CI)	P value	Model 2 β (95% CI)	P value	Model 3 β (95% CI)	P value	Model 4 β (95% CI)	P value
Anterior corpus callosum	-0.002 (-0.01, 0.01)	0.70	-0.01 (-0.02, 0.01)	0.37	0.004 (-0.01, 0.02)	0.58	0.003 (-0.01, 0.02)	0.71
Posterior corpus callosum	-0.01 (-0.02, 0.01)	0.43	-0.003 (-0.02, 0.01)	0.68	-0.01 (-0.02, 0.01)	0.30	-0.01 (-0.02, 0.01)	0.35
Frontal lobe	**-0.02 (-0.03, -0.01)**	**<0.0001**	**-0.01 (-0.02, -0.01)**	**0.0003**	-0.01 (-0.02, 0.002)	0.11	-0.01 (-0.01, 0.003)	0.18
Temporal lobe	0.001 (-0.01, 0.01)	0.88	-0.001 (-0.01, 0.01)	0.84	**-0.01 (-0.03, -0.003)**	**0.02**	**-0.02 (-0.03, -0.003)**	**0.01**
Occipital lobe	0.004 (-0.01, 0.02)	0.50	-0.002 (-0.01, 0.01)	0.76	0.003 (-0.01, 0.02)	0.68	0.001 (-0.01, 0.01)	0.83
Parietal lobe	0.01 (-0.002, 0.01)	0.15	**0.01 (0.002, 0.02)**	**0.01**	0.004 (-0.004, -0.01)	0.31	0.01 (-0.003, 0.01)	0.20

Bold indicates statistical significance. β is the difference (unadjusted for Model 1, adjusted for Model 2 to Model 4) of FAs between high and non-high cfPWV.

Model 1: Adjusted for FAs in other regions.

Model 2: Adjusted for volume of white matter hyperintensities.

Model 3: Adjusted for age, sex, race-center, education, APOE genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes, physical activity (total minutes/week), LDL-C, heart rate

Model 4: Adjusted for factors included in Model 2 and Model 3.

Table S7. Association of cfPWV and z-scores of MD (n=1484). Mean differences estimated by multivariable linear regression by cognitive status.

Regions	Cognitive status	cfPWV (m/s)							
		Model 1 β (95% CI)	P value	Model 2 β (95% CI)	P value	Model 3 β (95% CI)	P value	Model 4 β (95% CI)	P value
Anterior corpus callosum	Normal (n=937)	**0.04 (0.02, 0.06)**	**0.0003**	**0.03 (0.01, 0.05)**	**0.001**	**0.02 (0.003, 0.04)**	**0.02**	**0.02 (0.004, 0.04)**	**0.02**
	MCI/dementia (n=545)	**0.03 (0.01, 0.06)**	**0.01**	**0.03 (0.003, 0.05)**	**0.03**	0.03 (-0.001, 0.05)	0.06	0.02 (-0.001, 0.05)	0.06
Posterior corpus callosum	Normal (n=937)	0.02 (-0.004, 0.04)	0.12	0.01 (-0.01, 0.03)	0.19	**0.03 (0.01, 0.05)**	**0.01**	**0.02 (0.005, 0.04)**	**0.01**
	MCI/dementia (n=545)	0.02 (-0.01, 0.04)	0.15	0.01 (-0.01, 0.04)	0.23	0.02 (-0.01, 0.04)	0.18	0.02 (-0.01, 0.04)	0.20
Frontal lobe	Normal (n=937)	**0.05 (0.03, 0.07)**	**<0.0001**	**0.03 (0.01, 0.05)**	**0.001**	**0.03 (0.01, 0.05)**	**0.001**	**0.02 (0.01, 0.04)**	**0.005**
	MCI/dementia (n=545)	**0.05 (0.02, 0.07)**	**0.0003**	**0.02 (0.002, 0.05)**	**0.03**	0.03 (-0.001, 0.05)	0.06	**0.02 (0.0000, 0. 04)**	**0.05**
Temporal lobe	Normal (n=937)	**0.05 (0.03, 0.07)**	**<0.0001**	**0.03 (0.01, 0.05)**	**0.002**	**0.03 (0.02, 0.05)**	**<0.0001**	**0.03 (0.01, 0.04)**	**0.001**
	MCI/dementia (n=545)	**0.03 (0.002, 0.05)**	**0.03**	0.01 (-0.01, 0.03)	0.41	0.02 (-0.01, 0.04)	0.22	0.01 (-0.01, 0.04)	0.26
Occipital lobe	Normal (n=936)	**0.04 (0.02, 0.06)**	**<0.0001**	**0.03 (0.01, 0.05)**	**0.003**	**0.02 (0.002, 0.04)**	**0.03**	0.02 (-0.003, 0.03)	0.09
	MCI/dementia (n=545)	**0.04 (0.02, 0.07)**	**0.002**	**0.03 (0.002, 0.05)**	**0.02**	0.02 (-0.01, 0.04)	0.15	0.02 (-0.01, 0.04)	0.18
Parietal lobe	Normal (n=937)	**0.04 (0.02, 0.06)**	**0.0001**	0.02 (-0.002, 0.04)	0.08	**0.03 (0.01, 0.04)**	**0.005**	**0.02 (0.001, 0.03)**	**0.04**
	MCI/dementia (n=545)	**0.04 (0.01, 0.06)**	**0.01**	0.01 (-0.01, 0.04)	0.23	0.02 (-0.01, 0.05)	0.12	0.02 (-0.004, 0.04)	0.12
Overall	Normal (n=936)	**0.05 (0.03, 0.07)**	**<0.0001**	**0.03 (0.01, 0.05)**	**0.003**	**0.03 (0.01, 0.05)**	**0.001**	**0.02 (0.01, 0.04)**	**0.004**
	MCI/dementia (n=545)	**0.04 (-0.07, -0.02)**	**0.0003**	0.02 (-0.001, 0.04)	0.07	0.02 (-0.002, 0.05)	0.07	0.02 (-0.001, 0.04)	0.06

Bold indicates statistical significance. β is the difference (unadjusted for Model 1, adjusted for Model 2 to Model 4) of MDs between high and non-high cfPWV.

Model 1: Unadjusted.

Model 2: Adjusted for volume of white matter hyperintensities.

Model 3: Adjusted for age, sex, race-center, education, APOE genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes, physical activity (total minutes/week), LDL-C, heart rate

Model 4: Adjusted for factors included in Model 2 and Model 3.

Table S8. Association of cfPWV and z-scores of MD. Mean differences estimated by multivariable linear regression by WMH volumes

Regions	Cognitive status	cfPWV (m/s)							
		Model 1 β (95% CI)	P value	Model 2 β (95% CI)	P value	Model 3 β (95% CI)	P value	Model 4 β (95% CI)	P value
Anterior corpus callosum	High WMH volume (n=371)	**0.03 (0.01, 0.06)**	**0.02**	**0.03 (0.004, 0.06)**	**0.03**	0.02 (-0.01, 0.05)	0.14	0.02 (-0.01, 0.05)	0.15
	Low WMH volume (n=371)	0.04 (-0.001, 0.07)	0.05	0.03 (-0.01, 0.07)	0.09	**0.04 (0.01, 0.08)**	**0.01**	**0.04 (0.01, 0.08)**	**0.01**
Posterior corpus callosum	High WMH volume (n=371)	0.02 (-0.01, 0.05)	0.28	0.01 (-0.02, 0.04)	0.49	0.001 (-0.03, 0.03)	0.92	-0.002 (-0.03, 0.03)	0.87
	Low WMH volume (n=371)	0.001 (-0.03, 0.04)	0.94	0.0001 (-0.04, 0.04)	0.99	**0.03 (0.001, 0.07)**	**0.04**	**0.03 (0.001, 0.07)**	**0.05**
Frontal lobe	High WMH volume (n=371)	**0.06 (0.03, 0.09)**	**0.0002**	**0.04 (0.01, 0.06)**	**0.01**	**0.03 (0.01, 0.06)**	**0.02**	0.02 (-0.002, 0.05)	0.07
	Low WMH volume (n=371)	0.02 (-0.01, 0.05)	0.20	0.01 (-0.02, 0.04)	**0.01**	0.02 (-0.01, 0.04)	**0.05**	0.02 (-0.01, 0.04)	0.27
Temporal lobe	High WMH volume (n=371)	**0.05 (0.02, 0.07)**	**0.002**	**0.03 (0.004, 0.06)**	**0.03**	**0.03 (0.0004, 0.06)**	**0.05**	0.02 (-0.005, 0.05)	0.11
	Low WMH volume (n=371)	0.02 (-0.02, 0.05)	0.37	0.005 (-0.03, 0.04)	0.78	**0.03 (0.001, 0.05)**	**0.04**	0.02 (-0.002, 0.05)	0.06
Occipital lobe	High WMH volume (n=371)	**0.06 (0.03, 0.09)**	**<0.0001**	**0.05 (0.02, 0.08)**	**0.001**	**0.03 (0.01, 0.06)**	**0.02**	**0.03 (0.002, 0.06)**	**0.04**
	Low WMH volume (n=371)	0.01 (-0.03, 0.04)	0.72	-0.003 (-0.04, 0.03)	0.86	0.003 (-0.03, 0.03)	0.87	-0.0005 (-0.03, 0.03)	0.98
Parietal lobe	High WMH volume (n=371)	**0.05 (0.02, 0.08)**	**0.002**	0.03 (-0.001, 0.05)	0.06	0.03 (-0.004, 0.06)	0.08	0.01 (-0.01, 0.04)	0.27
	Low WMH volume (n=371)	0.003 (-0.03, 0.03)	0.85	-0.005 (-0.04, 0.03)	0.77	0.01 (-0.01, 0.04)	0.35	0.02 (-0.02, 0.04)	0.44
Overall	High WMH volume (n=371)	**0.06 (0.03, 0.09)**	**0.0002**	**0.04 (0.01, 0.06)**	**0.01**	**0.03 (0.005, 0.06)**	**0.02**	0.02 (-0.002, 0.05)	0.08
	Low WMH volume (n=371)	0.01 (-0.02, 0.05)	0.42	0.004 (-0.03, 0.04)	0.80	0.02 (-0.01, 0.04)	0.19	0.01 (-0.01, 0.04)	0.26

Bold indicates statistical significance. β is the difference (unadjusted for Model 1, adjusted for Model 2 to Model 4) of MDs between high and non-high cfPWV.

Model 1: Unadjusted.

Model 2: Adjusted for volume of white matter hyperintensities.

Model 3: Adjusted for age, sex, race-center, education, APOE genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes, physical activity (total minutes/week), LDL-C, heart rate

Model 4: Adjusted for factors included in Model 2 and Model 3.

Table S9. Association of cfPWV and MDs (n=1484). Mean differences estimated by multivariable linear regression with further adjustment for MDs of other locations

Regions	cfPWV (m/s)							
	Model 1 β (95% CI)	P value	Model 2 β (95% CI)	P value	Model 3 β (95% CI)	P value	Model 4 β (95% CI)	P value
Anterior corpus callosum	0.01 (-0.002, 0.02)	0.11	**0.02 (0.004, 0.03)**	**0.01**	0.004 (-0.01, 0.02)	0.53	0.01 (-0.01, 0.02)	0.43
Posterior corpus callosum	-0.01 (-0.02, 0.002)	0.10	-0.004 (-0.02, 0.01)	0.48	0.01 (-0.005, 0.02)	0.24	0.01 (-0.004, 0.02)	0.21
Frontal lobe	**0.01 (0.01, 0.02)**	**<0.0001**	**0.01 (0.005, 0.02)**	**0.001**	0.01 (-0.001, 0.01)	0.07	0.01 (-0.001, 0.01)	0.10
Temporal lobe	0.003 (-0.003, 0.01)	0.34	0.003 (-0.003, 0.01)	0.32	0.01 (-0.001, 0.01)	0.10	0.01 (-0.001, 0.01)	0.10
Occipital lobe	**0.01 (0.0003, 0.02)**	**0.04**	**0.01 (0.004, 0.02)**	**0.005**	-0.002 (-0.01, 0.01)	0.60	-0.002 (-0.01, 0.01)	0.69
Parietal lobe	**-0.01 (-0.01, -0.003)**	**0.003**	**-0.01 (-0.02, -0.01)**	**<0.0001**	-0.003 (-0.01, 0.002)	0.25	-0.004 (-0.01, 0.002)	0.17

Bold indicates statistical significance. β is the difference (unadjusted for Model 1, adjusted for Model 2 to Model 4) of MDs between high and non-high cfPWV.

Model 1: Adjusted for MDs in other regions.

Model 2: Adjusted for volume of white matter hyperintensities.

Model 3: Adjusted for age, sex, race-center, education, APOE genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes, physical activity (total minutes/week), LDL-C, heart rate

Model 4: Adjusted for factors included in Model 2 and Model 3.

Table S10. Association of high cfPWV (upper 25th percentile) and z-scores of FA. Mean differences estimated by multivariable linear regression

Regions	Elevated cfPWV (cfPWV≥13.65 m/s)							
	Model 1 β (95% CI)	P value	Model 2 β (95% CI)	P value	Model 3 β (95% CI)	P value	Model 4 β (95% CI)	P value
Anterior corpus callosum	**-0.35 (-0.55, -0.15)**	**0.001**	**-0.30 (-0.50, -0.10)**	**0.003**	**-0.30 (-0.51, -0.09)**	**0.01**	**-0.28 (-0.49, 0.07)**	**0.01**
Posterior corpus callosum	**-0.25 (-0.44, -0.07)**	**0.01**	-0.16 (-0.34, 0.02)	0.08	**-0.20 (-0.39, -0.01)**	**0.04**	-0.15 (-0.33, 0.03)	0.11
Frontal lobe	**-0.45 (-0.65, -0.25)**	**<0.0001**	**-0.29 (-0.47, -0.11)**	**0.002**	**-0.39 (-0.59, -0.18)**	**0.0002**	**-0.30 (-0.49, -0.12)**	**0.001**
Temporal lobe	-0.20 (-0.40, 0.01)	0.06	-0.10 (-0.31, 0.10)	0.31	**-0.34 (-0.55, -0.12)**	**0.002**	**-0.29 (-0.49, -0.08)**	**0.01**
Occipital lobe	**-0.29 (-0.50, -0.08)**	**0.01**	**-0.23 (-0.44, -0.02)**	**0.03**	**-0.31 (-0.52, -0.09)**	**0.01**	**-0.28 (-0.50, -0.06)**	**0.01**
Parietal lobe	**-0.31 (-0.51, -0.11)**	**0.002**	-0.15 (-0.33, 0.04)	0.12	**-0.32 (-0.53, -0.12)**	**0.002**	**-0.23 (-0.42, -0.05)**	**0.01**
Overall	**-0.40 (-0.61, -0.20)**	**<0.0001**	**-0.25 (-0.44, -0.06)**	**0.01**	**-0.40 (-0.61, -0.20)**	**0.0001**	**-0.32 (-0.51, -0.13)**	**0.001**

Bold indicates statistical significance. β is the difference (unadjusted for Model 1, adjusted for Model 2 to Model 4) of FAs between high and non-high cfPWV.

Model 1: Unadjusted.

Model 2: Adjusted for volume of white matter hyperintensities.

Model 3: Adjusted for age, sex, race-center, education, APOE genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes, physical activity (total minutes/week), LDL-C, heart rate

Model 4: Adjusted for factors included in Model 2 and Model 3.

Table S11. Association of high cfPWV (upper 25th percentile) and MDs. Mean differences estimated by multivariable linear regression.

Regions	Elevated cfPWV (cfPWV≥13.65 m/s)							
	Model 1 β (95% CI)	P value	Model 2 β (95% CI)	P value	Model 3 β (95% CI)	P value	Model 4 β (95% CI)	P value
Anterior corpus callosum	**0.35 (0.15, 0.55)**	**0.001**	**0.30 (0.10, 0.50)**	**0.003**	**0.26 (0.08, 0.44)**	**0.004**	**0.25 (0.07, 0.43)**	**0.01**
Posterior corpus callosum	**0.21 (0.01, 0.41)**	**0.04**	0.13 (-0.06, 0.33)	0.18	**0.22 (0.05, 0.39)**	**0.01**	**0.18 (0.02, 0.35)**	**0.03**
Frontal lobe	**0.41 (0.21, 0.62)**	**<0.0001**	**0.22 (0.04, 0.40)**	**0.02**	**0.27 (0.10, 0.45)**	**0.003**	**0.18 (0.02, 0.33)**	**0.02**
Temporal lobe	**0.31 (0.10, 0.51)**	**0.003**	0.16 (-0.03, 0.35)	0.10	**0.21 (0.04, 0.38)**	**0.01**	0.15 (-0.01, 0.31)	0.06
Occipital lobe	**0.33 (0.13, 0.53)**	**0.001**	**0.22 (0.03, 0.42)**	**0.02**	**0.19 (0.01, 0.36)**	**0.03**	0.14 (-0.03, 0.31)	0.10
Parietal lobe	**0.33 (0.13, 0.53)**	**0.001**	0.15 (-0.03, 0.33)	0.11	**0.27 (0.10, 0.43)**	**0.002**	**0.18 (0.04, 0.32)**	**0.01**
Overall	**0.38 (0.18, 0.58)**	**0.0002**	**0.20 (0.02, 0.39)**	**0.03**	**0.27 (0.10, 0.43)**	**0.002**	**0.18 (0.04, 0.33)**	**0.01**

Bold indicates statistical significance. β is the difference (unadjusted for Model 1, adjusted for Model 2 to Model 4) of MDs between high and non-high cfPWV.

Model 1: Unadjusted.

Model 2: Adjusted for volume of white matter hyperintensities.

Model 3: Adjusted for age, sex, race-center, education, APOE genotype, ever smoking, ever drinking, body mass index, mean arterial pressure, diabetes, physical activity (total minutes/week), LDL-C, heart rate

Model 4: Adjusted for factors included in Model 2 and Model 3.

Figure S1. Flowchart of participant selection.

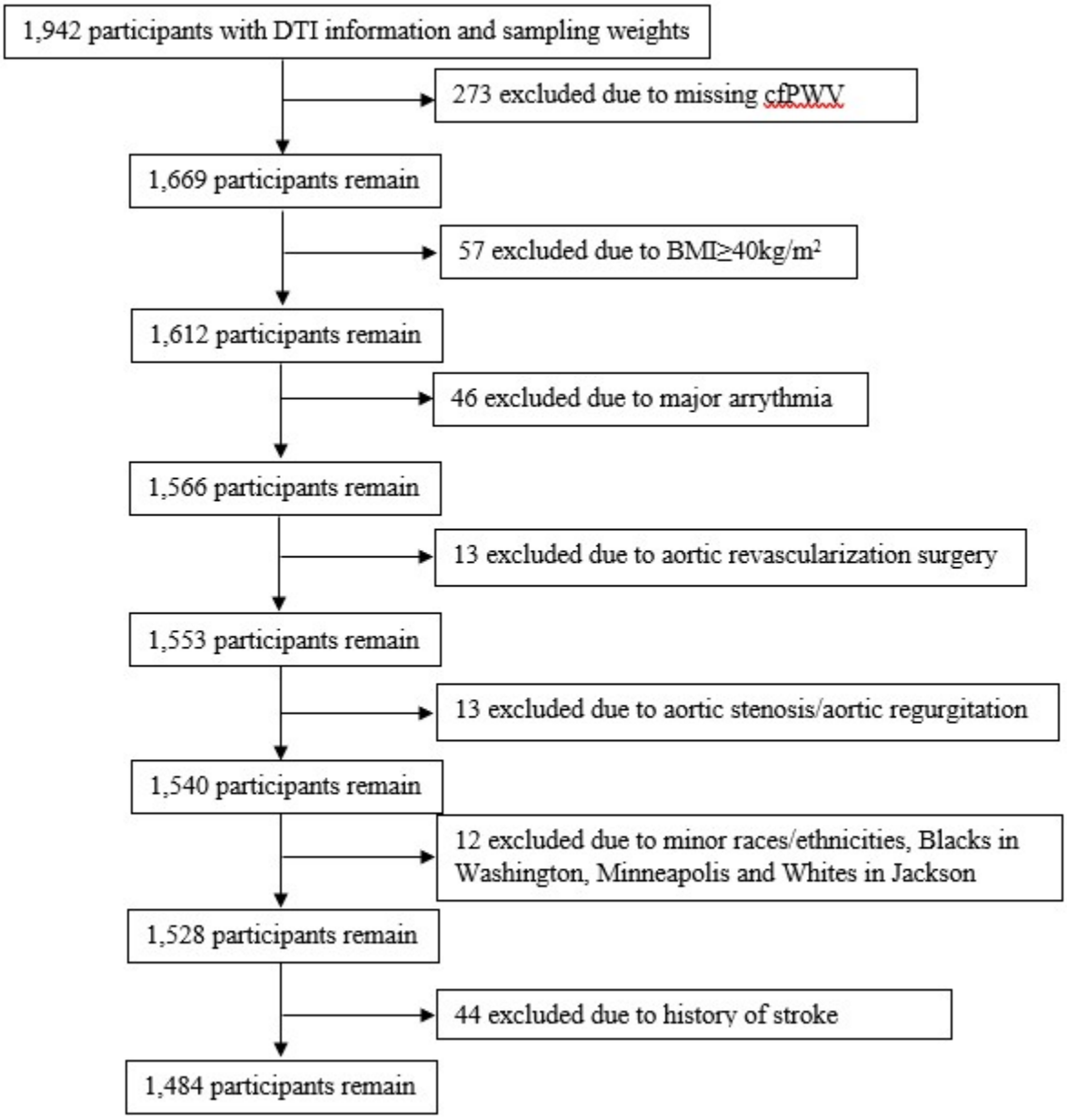
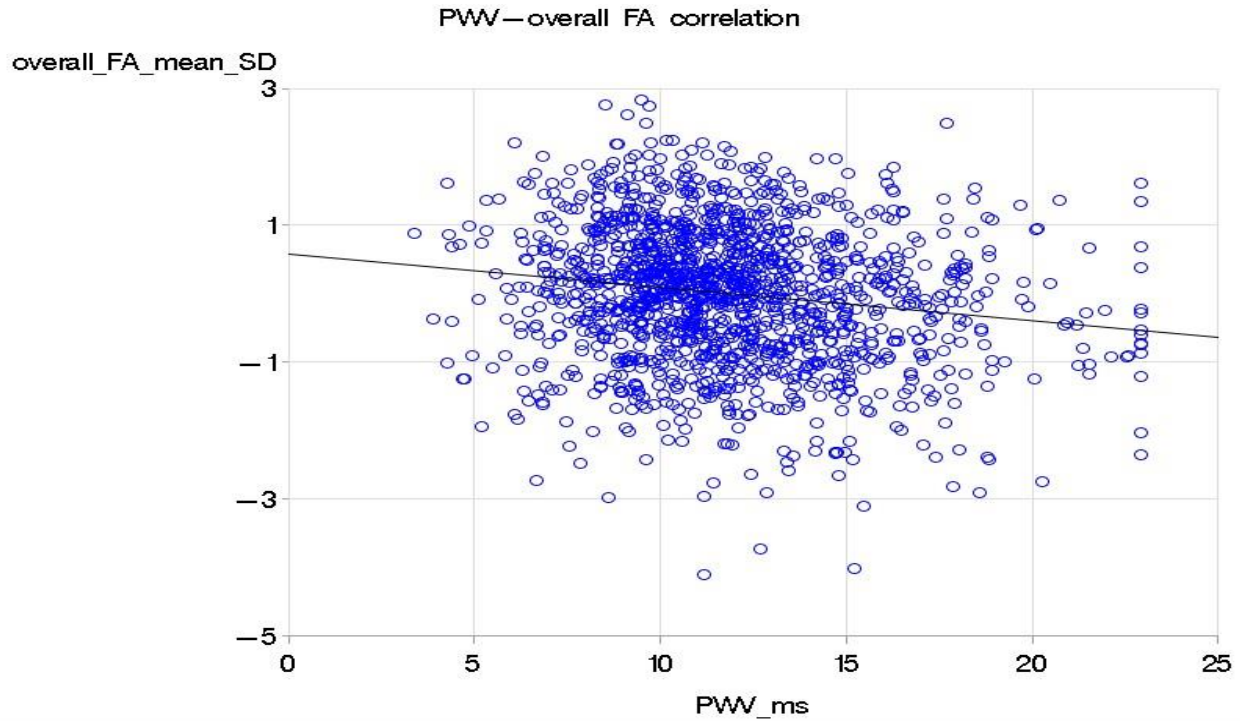
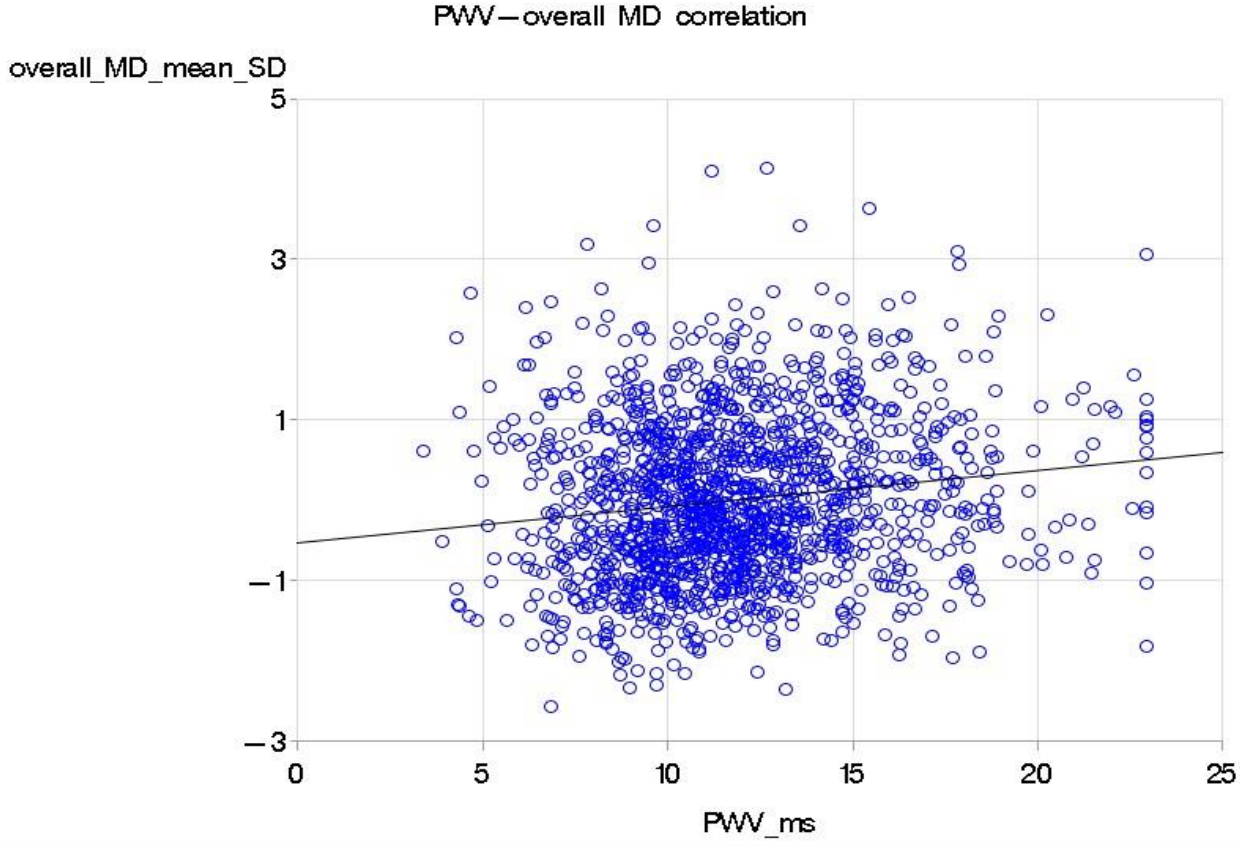
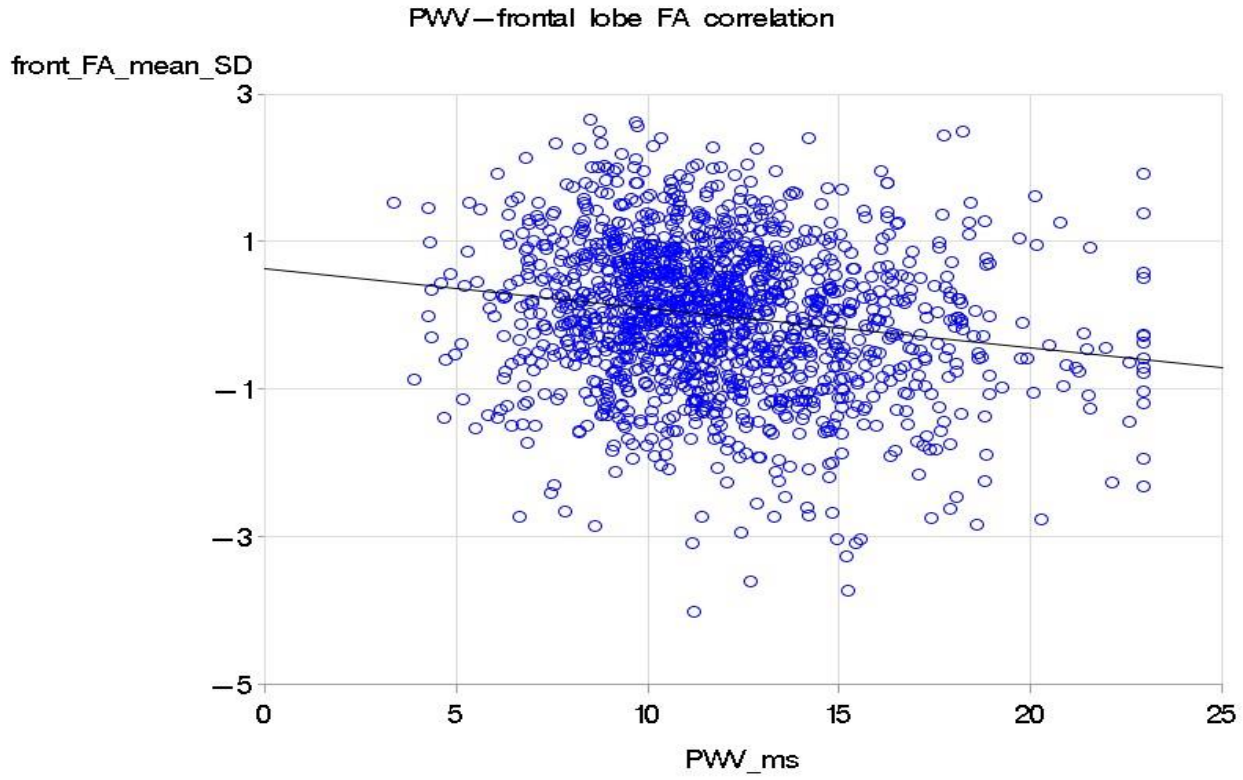


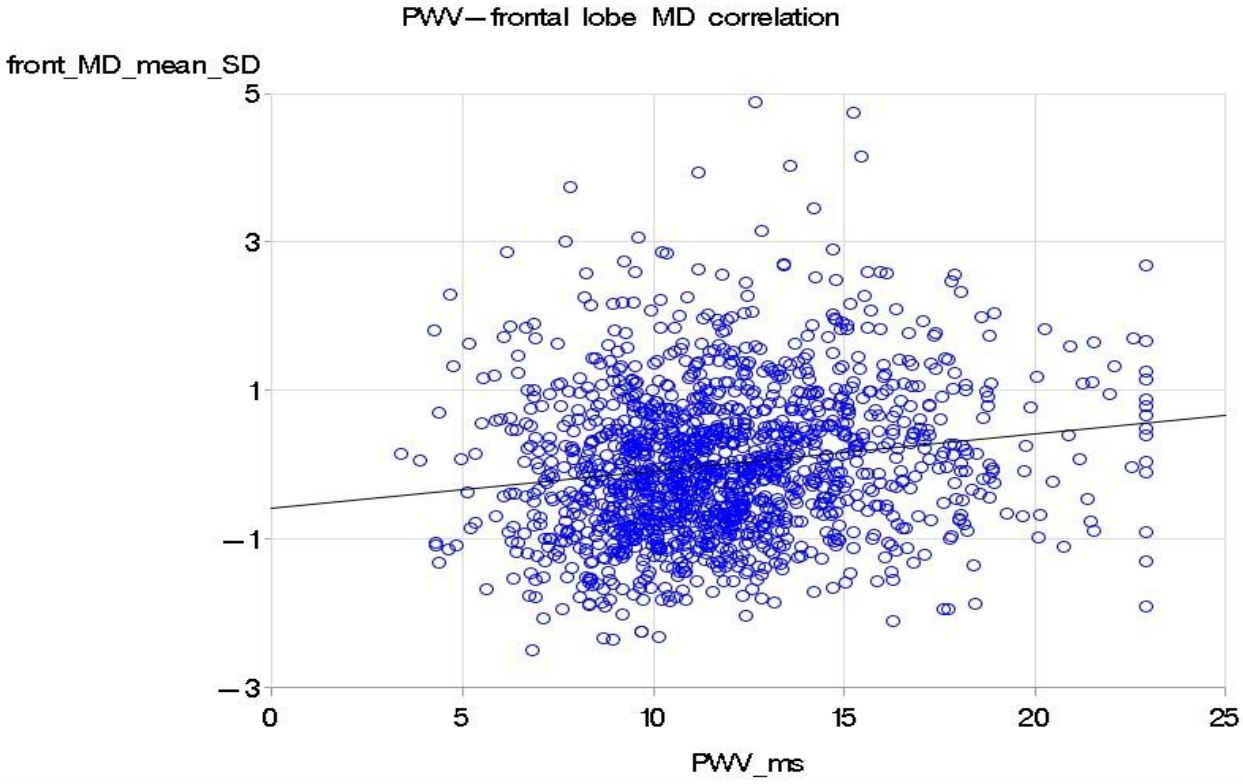
Figure S2. Scatter plot of correlation between cfPWV and white matter microstructural integrity in (A) overall (B) frontal lobe (C) temporal lobe (D) occipital lobe (E) parietal lobe (F) anterior corpus callosum (G) posterior corpus callosum.



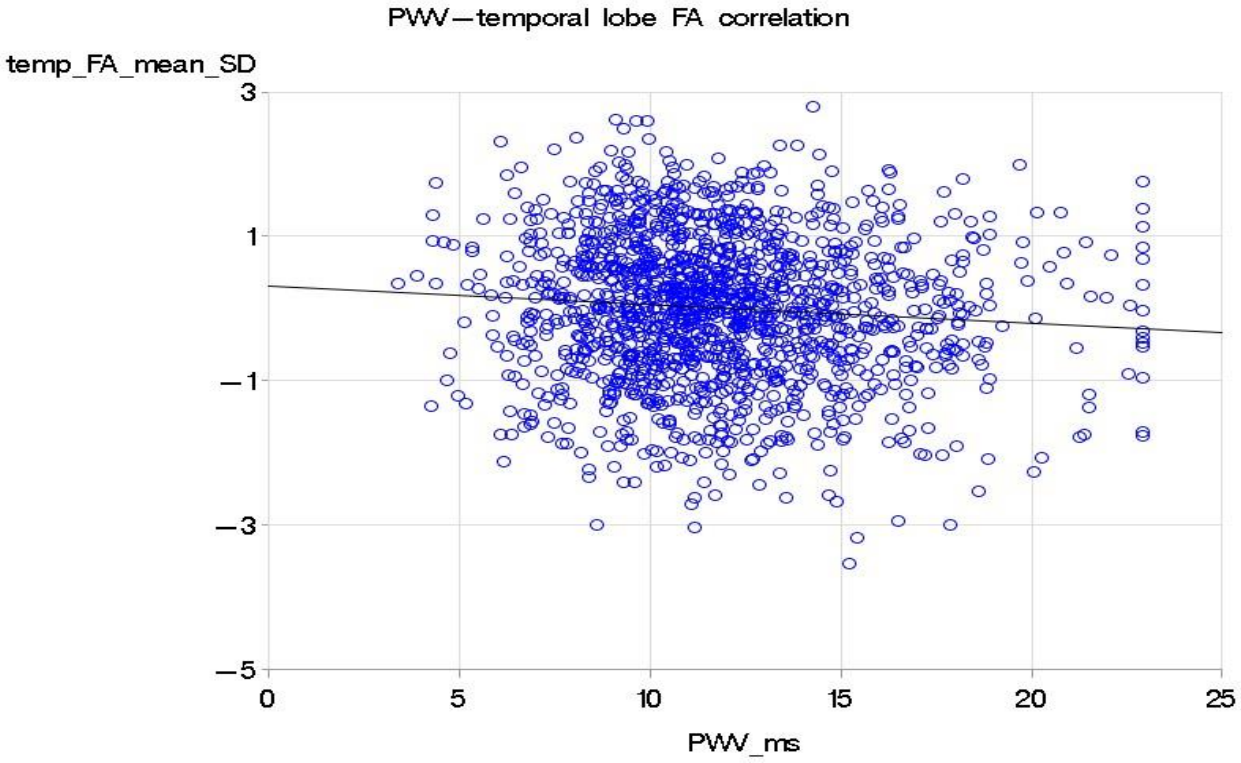


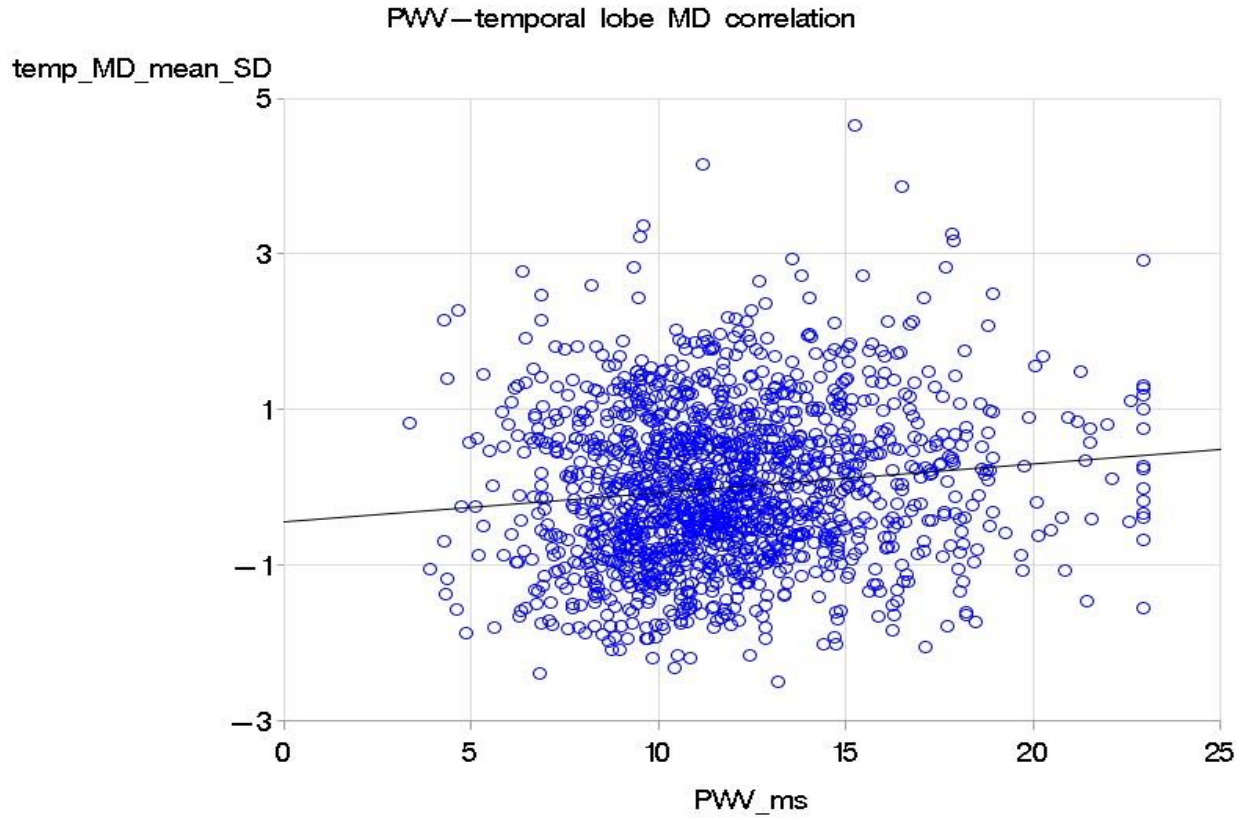
(A)


PWV—frontal lobe FA correlation
front_FA_mean_SD
3
1
−1
−3
−5
0
5
10
15
20
25
PWV_ms

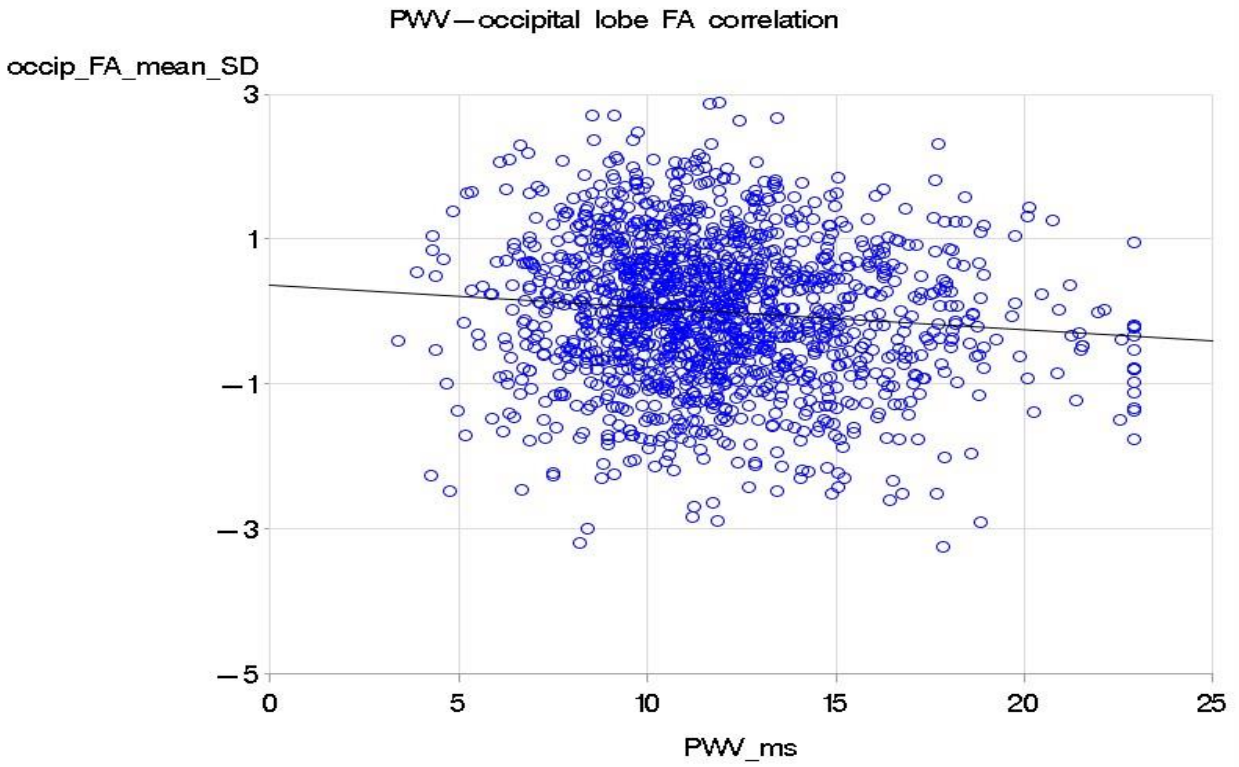

PWV—frontal lobe MD correlation
front_MD_mean_SD
5
3
1
−1
−3
0
5
10
15
20
25
PWV_ms

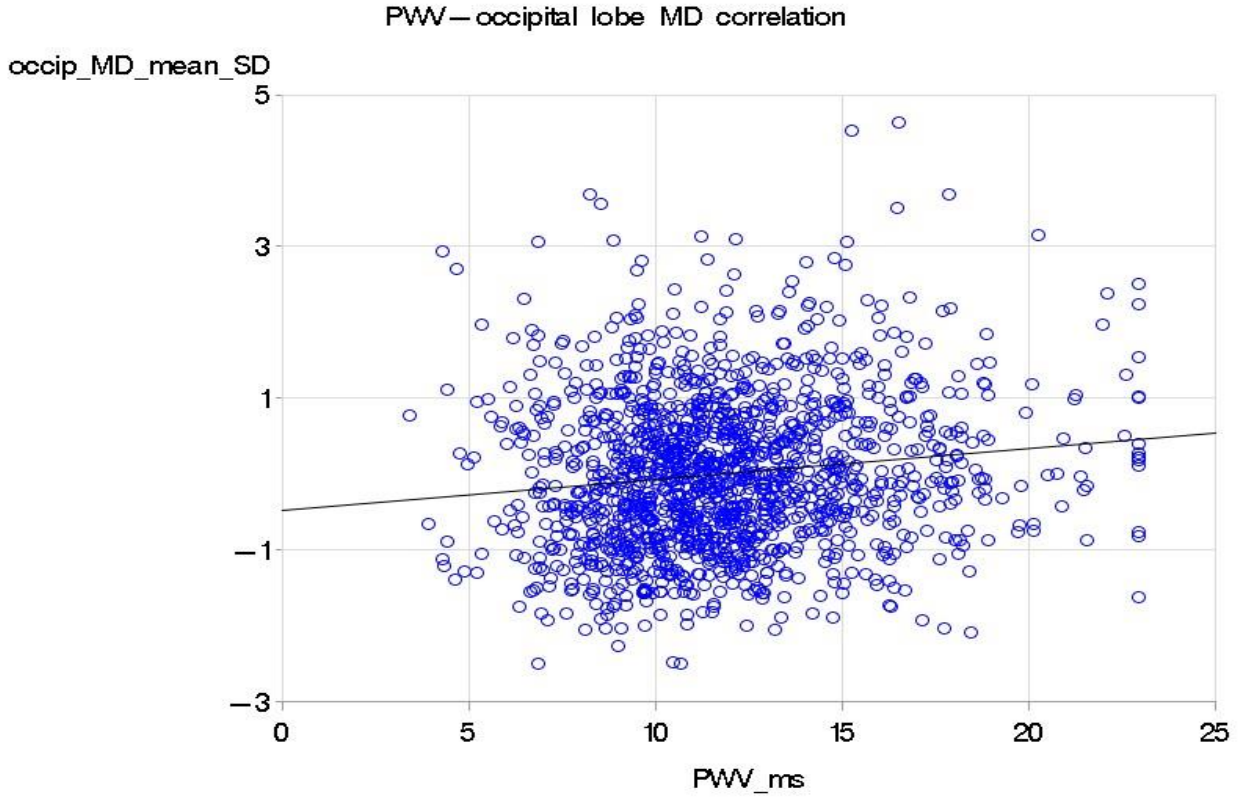
(B)


PWV—temporal lobe FA correlation
temp_FA_mean_SD
3
1
−1
−3
−5
0
5
10
15
20
25
PWV_ms

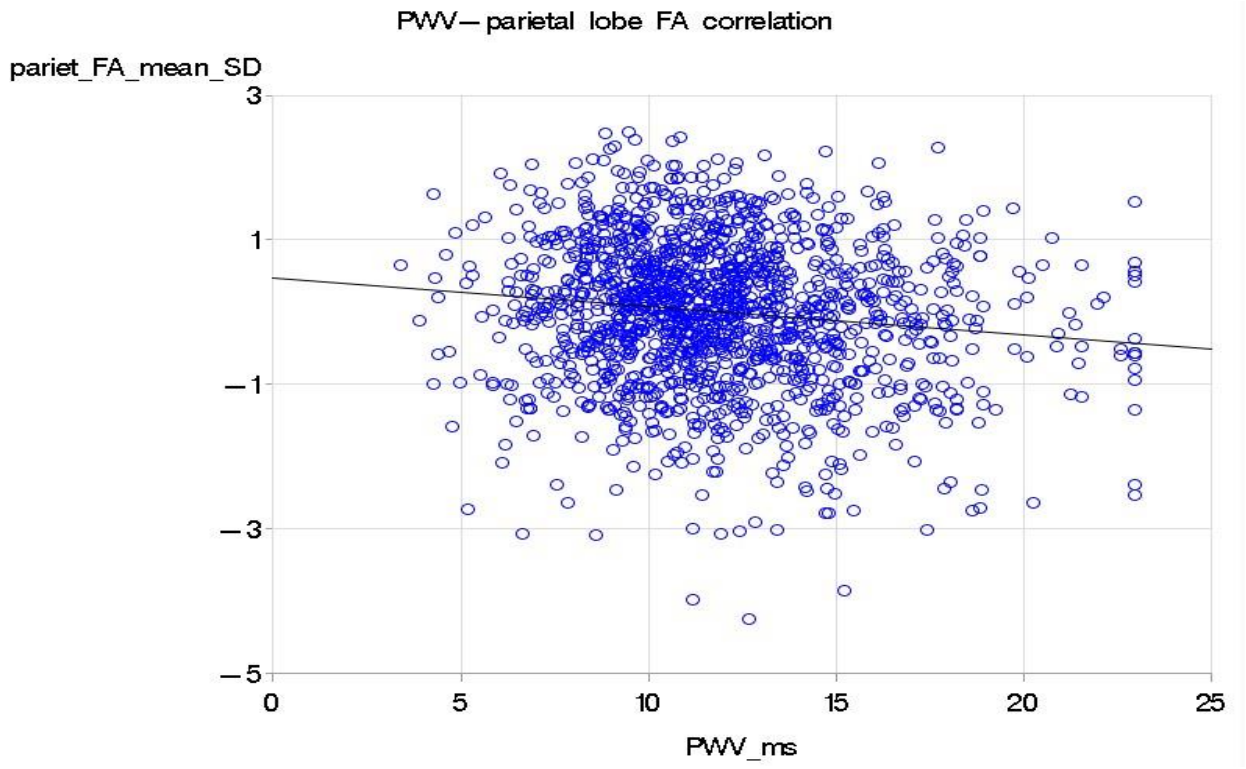

PWV—temporal lobe MD correlation
temp_MD_mean_SD
5
3
1
−1
−3
0
5
10
15
20
25
PWV_ms

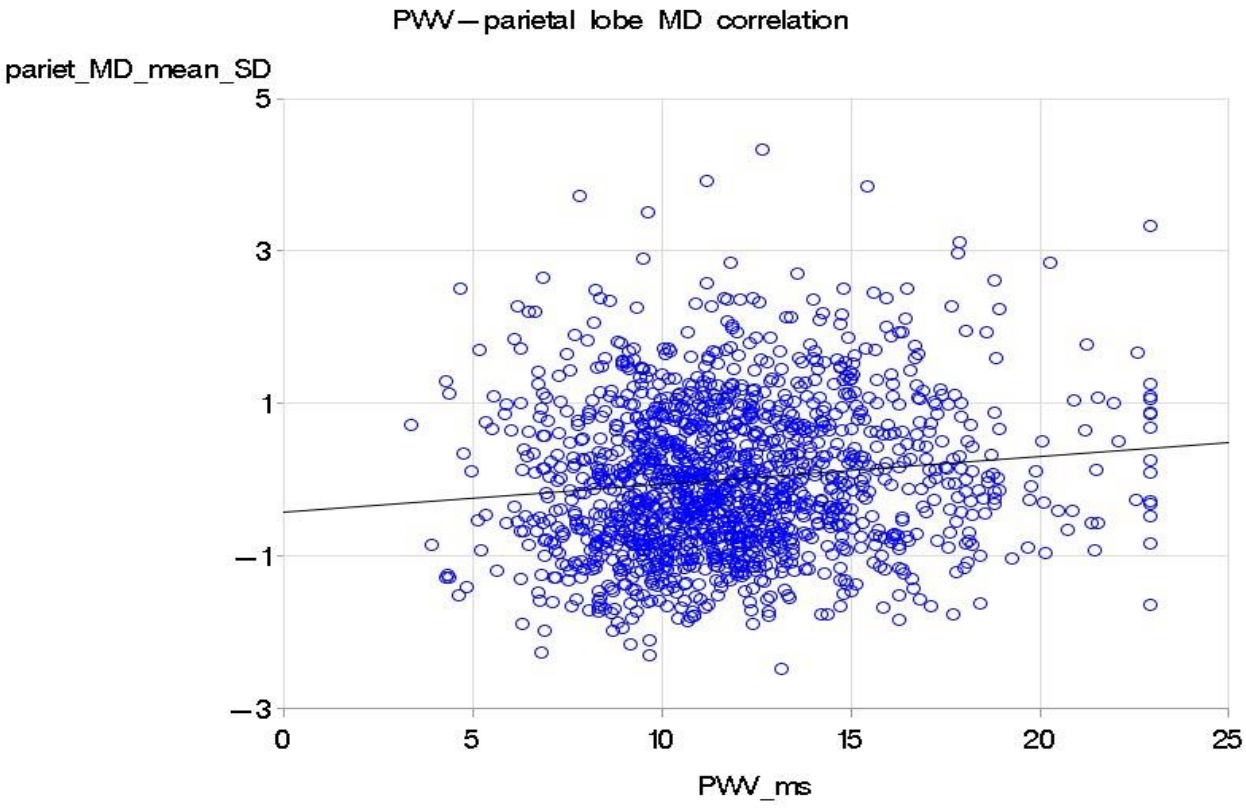
(C)


PWV—occipital lobe FA correlation
occip_FA_mean_SD
3
1
−1
−3
−5
0
5
10
15
20
25
PWV_ms

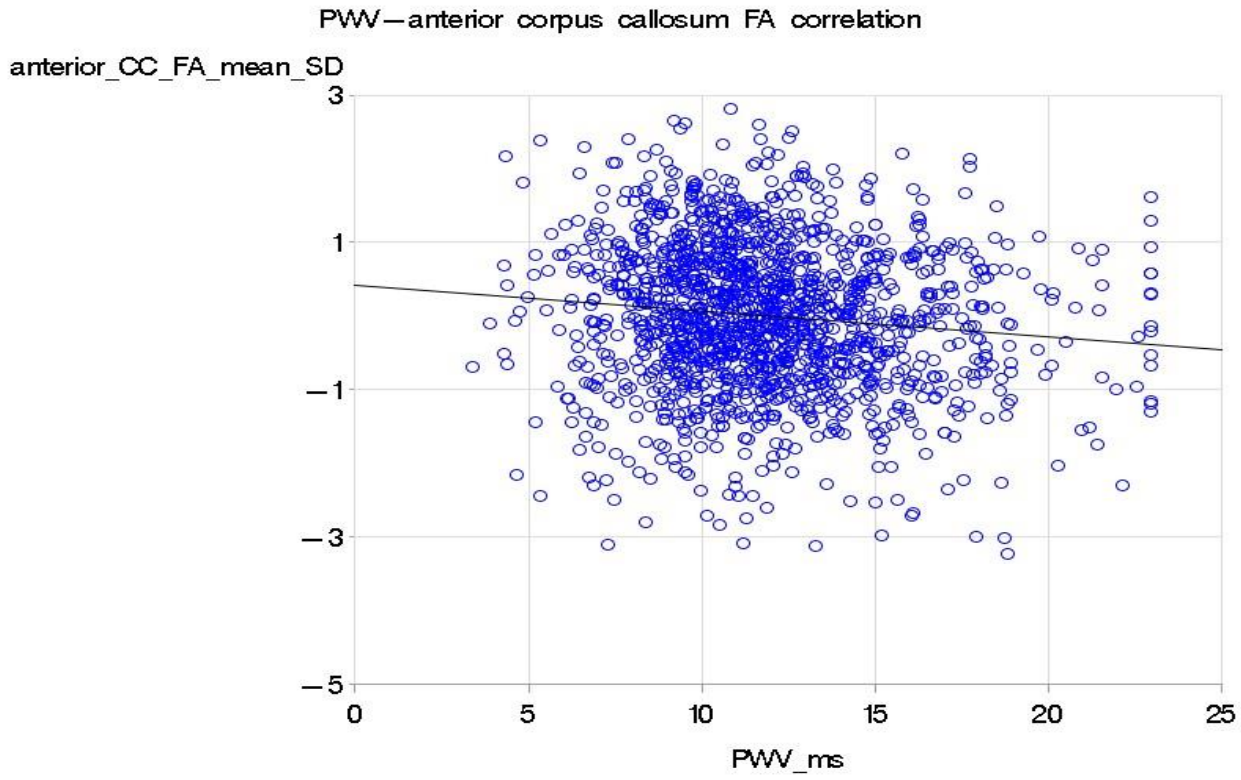

PWV—occipital lobe MD correlation
occip_MD_mean_SD
5
3
1
−1
−3
0
5
10
15
20
25
PWV_ms

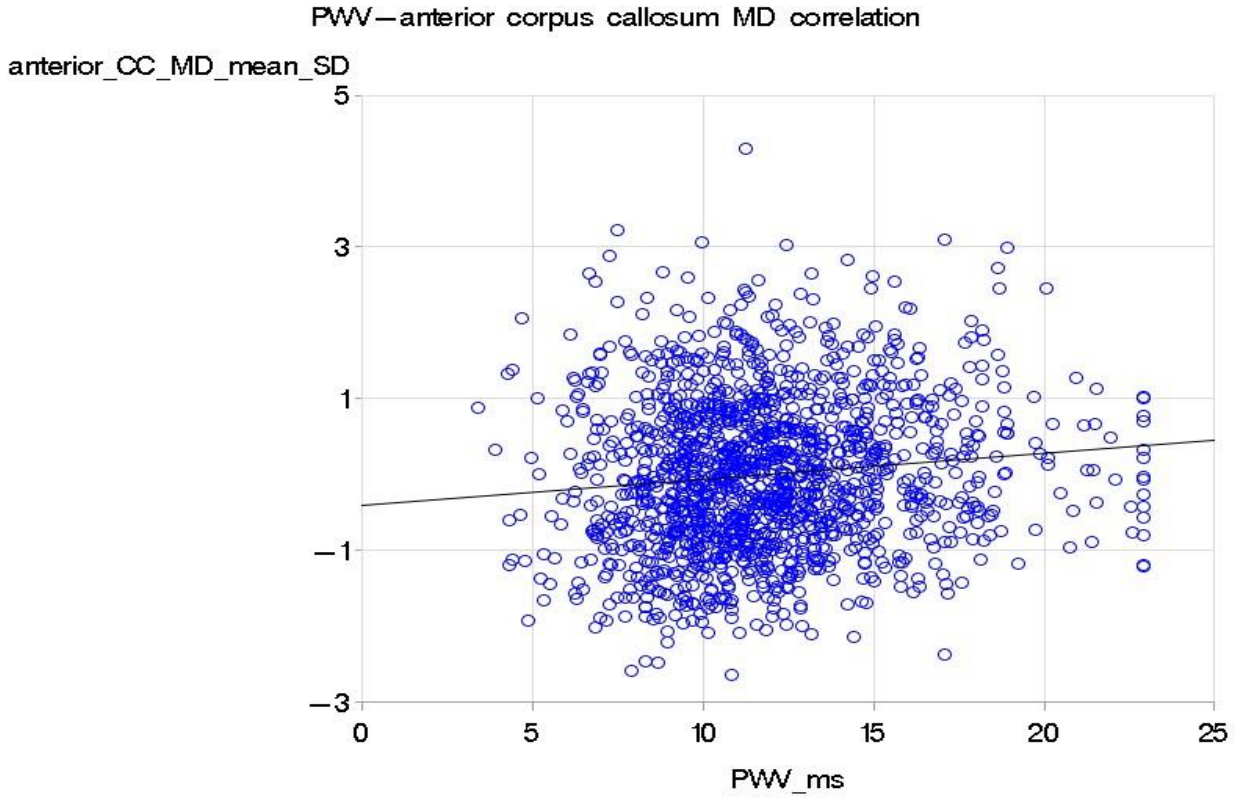
(D)


PWV—parietal lobe FA correlation
pariet_FA_mean_SD
3
1
−1
−3
−5
0
5
10
15
20
25
PWV_ms

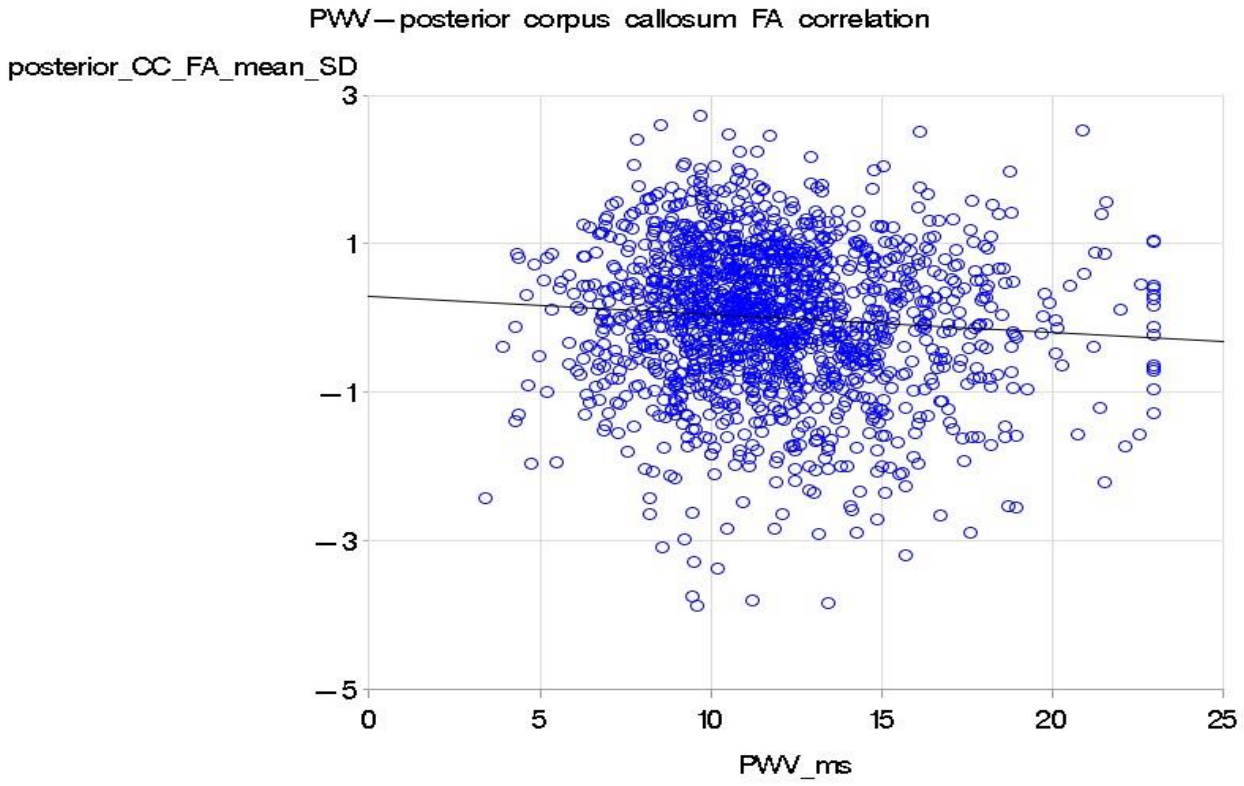

PWV—parietal lobe MD correlation
pariet_MD_mean_SD
5
3
1
−1
−3
0
5
10
15
20
25
PWV_ms

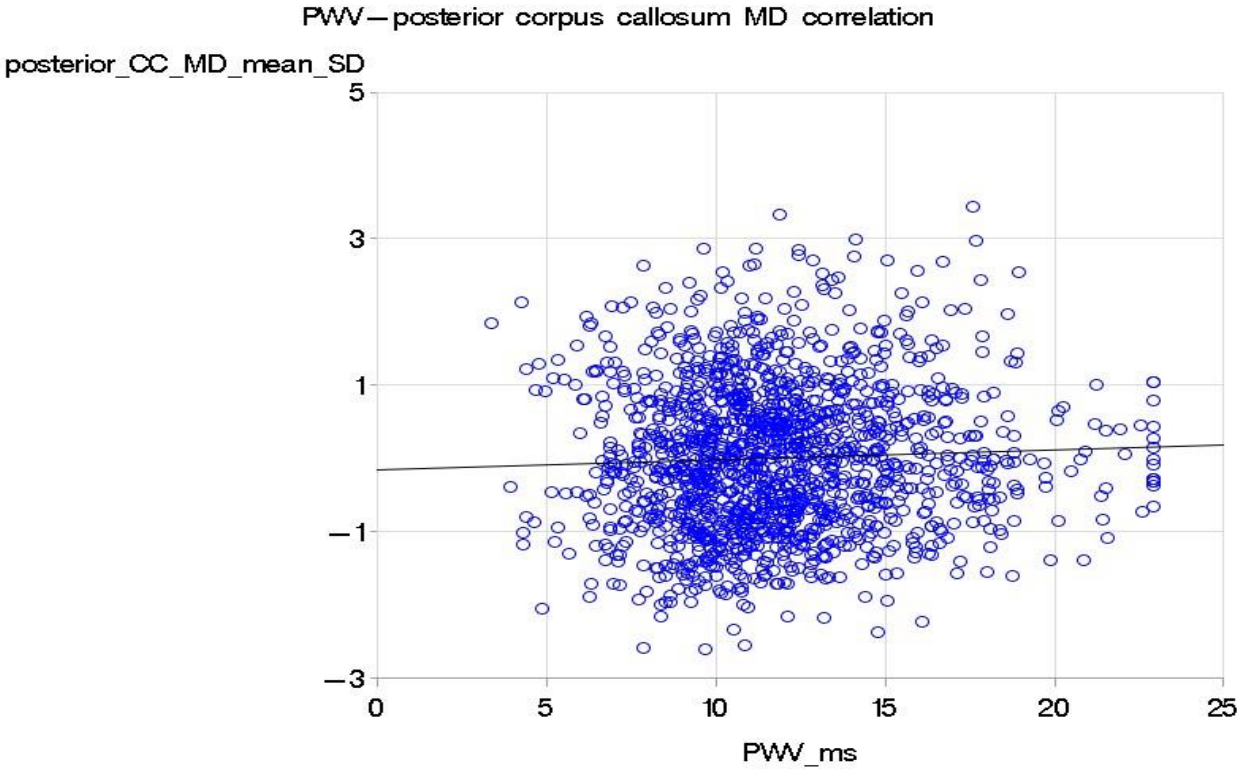
(E)


PWV—anterior corpus callosum FA correlation
anterior_CC_FA_mean_SD
3
1
−1
−3
−5
0
5
10
15
20
25
PWV_ms


PWV—anterior corpus callosum MD correlation
anterior_CC_MD_mean_SD
5
3
1
−1
−3
0
5
10
15
20
25
PWV_ms

(F)


PWV—posterior corpus callosum FA correlation
posterior_CC_FA_mean_SD
3
1
−1
−3
−5
0
5
10
15
20
25
PWV_ms


PWV—posterior corpus callosum MD correlation
posterior_CC_MD_mean_SD
5
3
1
−1
−3
0
5
10
15
20
25
PWV_ms

(G)