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RESEARCH ARTICLE

Vascular and microstructural markers of cognitive pathology

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Abstract

Introduction: Arterial stiffness may play a role in the development of dementia through poorly understood effects on brain microstructural integrity and perfusion.

Methods: We examined markers of arterial stiffness (carotid-femoral pulse wave velocity [cfPWV]) and elevated systolic blood pressure (SBP) in relation to cognitive function and brain magnetic resonance imaging macrostructure (gray matter [GM] and white matter [WM] volumes), microstructure (diffusion based free water [FW] and fractional anisotropy [FA]), and cerebral blood flow (CBF) in WM and GM in models adjusted for age, race, sex, education, and apolipoprotein E ε4 status.

Results: Among 460 participants (70 $\pm$ 8 years; 44 dementia, 158 mild cognitive impairment, 258 normal cognition), higher cfPWV and SBP were independently associated with higher FW, higher WM hyperintensity volume, and worse cognition (global and executive function). Higher SBP alone was significantly associated with lower WM and GM CBF.

Discussion: Arterial stiffness is associated with impaired WM microstructure and global and executive cognitive function.

KEYWORDS
arterial stiffness, cognition, hypertension, magnetic resonance imaging, neuroimaging, neurite orientation density and dispersion imaging, white matter

1 | BACKGROUND

The number of people living with dementia is estimated to reach more than one hundred million globally by 2050,[1] highlighting the demand for novel prevention strategies. While Alzheimer's disease (AD) is the most common form of dementia, autopsy studies report fewer than half (41%) of individuals with clinically diagnosed AD show pathologic AD alone;[2] the vast majority (75%) have concomitant cerebrovascular pathology,[3] primarily in the form of cerebral small vessel disease. As its biological heterogeneity becomes increasingly evident, identifying the root causes of dementia-related pathology is necessary to define pathological pathways for intervention. Targeting vascular health for delaying dementia onset is recognized as a critical goal for AD and AD and related dementias (ADRD)[1,4,5] and has led to intense interest in the vascular contributions to cognitive impairment and dementia (VCID).

Arterial stiffness is emerging as a potential target for prevention of both VCID and ADRD through observed associations with cognitive decline, incidence of mild cognitive impairment (MCI), and dementia.[1,6] Arterial stiffness is an age-related vascular disorder accelerated by cardiometabolic risk factors.[7] Its effects on brain function are postulated to be due to excess pulsatility transmitted to the microvasculature of the brain.[7] Increased arterial stiffness escalates the potential effects of hypertension and elevated systolic blood pressure (SBP) on the brain; as such, hypertensive individuals are at greater risk for damage to white matter (WM) structures.[7,8] Arterial stiffness is associated with alterations in cerebral blood flow (CBF) and subsequent damage to WM via hypoperfusion, promoting the development of white matter hyperintensities (WMH).[8–10] Pulse wave velocity (PWV) is the gold standard for measuring arterial stiffness and is the most robust predictor of cerebrovascular risk.[8] PWV is associated with various subclinical hemodynamic and structural brain changes in the WM, including: excess pulsatile pressure in the carotid and large intracranial arteries,[11] microvascular hypoperfusion,[10,12] impaired cerebrovascular reactivity[10], microstructural WM abnormalities,[8] and various forms of small vessel disease.[11] Arterial stiffness is also associated with AD-specific biomarkers including elevated cerebrospinal fluid (CSF) levels of phosphorylated tau and neuroinflammation,[13] as well as amyloid beta (Aβ) deposition and its progression over time.[14,15] Arterial stiffness increases the risk for incident dementia[16,17] and of co-occurrence of multiple lesion types and "mixed dementia" within an individual.[14]

PWV shows less consistent relationships to other aspects of brain structure and perfusion. Studies describe consistent associations between PWV and higher WMH volume;[8,18,19] however, research relating PWV to CBF[9,10,20] and cortical thickness[21] is inconsistent. Higher PWV has also been associated with microstructural changes to WM integrity such as higher free water (FW) using neurite orientation density and dispersion imaging (NODDI)[12] and decreased fractional anisotropy (FA) using diffusion tensor imaging (DTI).[8,18,22] Notably, very few studies have compared PWV with NODDI metrics, which provide more specificity than DTI and might be more sensitive markers of early dementia pathology.[22] These microstructural changes are thought to precede macrostructural changes, as well as clinical symptoms.[23]

Higher arterial stiffness may translate to worse cognitive performance. Arterial stiffness has been shown to be higher in AD than in MCI or normal cognition.[24] Additionally, people with higher arterial stiffness perform worse on tests of executive function.[24] These effects on cognition are presumed to occur through the effect of vascular risk factors (arterial stiffness and hypertension) on brain microstructure and macrostructure.[8,25,26] For example, decreased FA is associated with worse cognitive function, depending on the brain region studied.[22,26]

Herein, we explore the connections of PWV (as a measure of arterial stiffness) and SBP (as a measure of blood pressure) with brain structure, hypoperfusion, and cognitive function to better understand these associations. Confirming and evaluating the relationships among arterial stiffness, brain structural changes, and cognitive impairment will allow us to better characterize vascular markers as manageable risk factors for dementia.

RESEARCH IN CONTEXT

1. **Systematic Review**: The authors reviewed the literature using PubMed and meeting abstracts and presentations. The relationship between cardiovascular risk factors and late-life brain health is poorly understood, particularly among diverse groups of older adults. Several recent studies have begun to investigate this question, using imaging biomarkers of disease and cognitive testing; these relevant citations are appropriately cited.
2. **Interpretation**: This adds to a growing literature showing that vascular hemodynamics (e.g., arterial stiffness and elevated blood pressure) are associated with structural and functional abnormalities in the brain, including multiple forms of dementia-related pathology (cerebral small vessel disease, lower cerebral blood flow, and increased Alzheimer's disease [AD] pathology) that underlie age-related cognitive disorders of AD and related dementias.
3. **Future Directions**: Future studies should evaluate arterial stiffness as a target for prevention of cerebral small vessel disease and cognitive decline in older adults.

2 | METHODS

2.1 | Participants

Participants were enrolled in the Wake Forest Alzheimer's Disease Research Center (ADRC) Clinical Core. Adults between the ages of 55 and 85 were recruited into the Clinical Core from the surrounding community between 2016 and 2021 and underwent standard evaluation including the National Alzheimer's Coordinating Center (NACC)

protocol for clinical data collection, clinical exams, neurocognitive testing, neuroimaging, and genotyping for apolipoprotein E (*APOE*) ε4. *APOE* genotype was obtained by Taqman using single nucleotide polymorphisms (rs429358 and rs7412) to determine haplotypes of ε2, ε3, and ε4. *APOE* ε4 was dichotomized to the presence or absence of one or more ε4 alleles. Race was self-reported as a social construct. Exclusion criteria for the Clinical Core included: large vessel stroke (participants with lacunae or small vessel ischemic disease were eligible); other significant neurologic diseases that might affect cognition other than AD; evidence of organ failure, active cancer treatment, uncontrolled clinical depression, or psychiatric illness; current use of insulin; and history of substance abuse or heavy alcohol consumption within previous 10 years. All activities described were approved by the Wake Forest Institutional Review Board. Written informed consent was obtained for all participants and/or their legally authorized representative.

2.2 | Blood pressure and hypertension

Brachial blood pressure was measured in a seated position after a 5-minute rest in a quiet and dark room using a DINAMAP automated blood pressure device (GE Healthcare). If the initial blood pressure reading was >160 mmHg SBP or 90 mmHg diastolic blood pressure, a second blood pressure was measured after another 5-minute rest. Blood pressure was categorized according to 2017 American College of Cardiology/American Heart Association guidelines[27] and hypertension status was defined as SBP ≥ 130 mmHg, diastolic blood pressure ≥80 mmHg, and/or the current use of antihypertensive medications.

2.3 | Medications

Participants provided a list of all prescription and over-the-counter medications taken. Participants considered to be on anti-hypertensive therapy took antiadrenergic agents, angiotensin converting enzyme inhibitors, beta-blockers, calcium channel blocking agents, diuretics, vasodilators, angiotensin II inhibitors, or antihypertensive combination therapy agents.

2.4 | Arterial assessment

Clinical Core participants underwent vascular assessments at baseline visits after a minimum 6-hour fast and 5-minute rest using the SphygmoCor Xcel to obtain: brachial blood pressure and PWV. Carotid-femoral PWV (cfPWV) was assessed in a supine position after a 5-minute rest. The linear distances measured distance from the carotid artery probe to a femoral thigh cuff at the site of the femoral artery. The linear velocity of cfPWV was measured twice in meters per second (m/s) and averaged. The reproducibility of cfPWV with this device was high in our pilot studies (intra-class correlation coefficient = 0.90) and similar to previous reports.[28]

2.5 | Magnetic resonance imaging acquisition and processing

Participants were scanned on a research-dedicated 3-Tesla Siemens Skyra magnetic resonance imaging (MRI; 32-channel head coil). Briefly, T1, T2 fluid-attenuated inversion recovery (FLAIR), DTI/NODDI, and Arterial Spin Labeling scans were acquired; detailed image acquisition parameters are available in the supporting information.[29–36] T1 processing included normalization and tissue segmentation using SPM12 (www.fil.ion.ucl.ac.uk/spm) CAT12. Cortical thickness was calculated on T1 using FreeSurfer v5.3 (https://surfer.nmr.mgh.harvard.edu) for a temporal region of interest (ROI; bilateral entorhinal, inferior/middle temporal, fusiform).[37] Total intracranial volume was also calculated. WMH volume (WMHv; lesions of presumed ischemic origin) were segmented by the lesion growth algorithm (LGA) implemented in the LST[38] toolbox v2.0.15, running in SPM12 using FLAIR and T1. WMH masks were edited by trained observers as needed. DTI and NODDI processing details are available in the supporting information; briefly, the Johns Hopkins University (JHU) DTI atlas[32] was overlaid on template-space FA and FW images to extract mean signal across all supratentorial WM tracts. Similarly, additional details on Arterial Spin Labeling image processing are available in the supporting information. For each participant, a set of all supratentorial Automated Anatomical Labeling gray matter (GM) ROIs were overlaid on template-space GM CBF images to calculate mean global GM CBF, and a set of all supratentorial JHU WM tracts were overlaid on template-space WM CBF images to calculate mean global WM CBF.

2.6 | Cognitive testing

Participants completed cognitive testing with the Uniform Data Set Version 3 (UDSv3)[39] test battery, including: Montreal Cognitive Assessment (MoCA), Craft Story, Benson Figure, Number Span, Phonemic Fluency (letters C, F, and L), Category Fluency (Animals and Vegetables), Trail Making Test A and B, and the Multilingual Naming Test; as well as supplemental tests commonly used to estimate current and past cognitive status (Mini-Mental State Examination [MMSE], American National Adult Reading Test) and to more deeply characterize performances in the domains of executive functioning and processing speed (Digit Symbol Coding [DSC] Test) and memory (Free and Cued Selective Reminding Test [FCSRT], Rey Auditory Verbal Learning Test). Subjective questionnaires assessing mood and perceived change in cognitive symptoms were administered including the 15-item Geriatric Depression Scale; the Clinical Dementia Rating (CDR) scale; and the Functional Assessment Questionnaire, which was used to estimate independence in managing activities of daily living.

UDSv3 cognitive test scores were normalized to create z-scores based on age, self-reported race, sex, and education.[39] Z-scores were then combined to create domain specific cognitive performance for: executive function, memory, language, attention, and visuospatial domains, according to Weintraub et al.[40] A modified Preclinical Alzheimer's Cognitive Composite (PACC5)[41] was created from five

cognitive tests: MMSE, FCSRT, Craft Story delayed verbatim recall, Digit Symbol Substitution Test, and category fluency.

2.7 | Adjudication

Adjudication of cognitive diagnosis by expert panel consensus occurred after review of all available clinical, neuroimaging, and cognitive data in accordance with current National Institute on Aging–Alzheimer's Association guidelines for diagnosis of MCI,[42] AD, and their subtypes.[43] The panel consisted of investigators with extensive experience assessing cognitive status and identifying cognitive impairment in older adults, including neuropsychologists, neurologists, and geriatricians.

2.8 | Statistical analysis

The analytic sample was restricted to 458 participants with arterial assessments and data from cognitive testing, at least one of the five MRI measures of interest for MRI analyses, and covariates of age, sex, and race. Race was self-reported and included as a covariate in analyses as a social, and not biological, construct. Participant demographics were compared across cognitive status groups using chi-square tests and one-way analysis of variance. Hypertension was defined as being on antihypertensive medications or Stage 1 or Stage 2 hypertension according to blood pressure; hypertension was a dichotomized (presence or absence) in these analyses. Models of cognitive performance with cfPWV and SBP separately as independent variables were considered first in unadjusted models because cognitive performance scores were already normed for age, sex, education, and race. A log transformation was applied to WMHv adjusted for total intracranial volume to account for its skewed distribution. Multivariable general linear models examined relationships between brain imaging variables, cfPWV and SBP, adjusting for covariates. All regression models included standardized, normally distributed, continuous measures of cfPWV and SBP so that regression coefficients correspond to a one standard deviation increase in PWV or SBP. Effect modification was assessed with interaction terms with primary predictors SBP and cfPWV and covariates cognitive status, age (median split), sex, *APOE* $\varepsilon 4$, and race. All statistical tests were conducted with SAS v9.4 using a significance level of $\alpha = 0.05$.

3 | RESULTS

3.1 | Demographics, vascular measures, and cognitive status

In total, 458 participants completed brain MRI, cognitive testing, adjudicated cognitive outcome, and arterial stiffness measurements. The mean age of participants was 70 ± 8 years, 14.7% were Black, 44% were adjudicated to have cognitive impairment (44 dementia, 158 MCI), and 45.7% were treated with anti-hypertensive medications. Participant demographic characteristics are summarized in Table 1. We observed

TABLE 1 Demographics and neurocognitive assessments by cognitive status

		Normal cognition (n = 257)		Mild cognitive impairment (n = 157)		Dementia (n = 44)		
		N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	*P*-value
Age (years)		68.6	8.1	71.8	7.7	74.4	8.2	< 0.001
Women		190	74%	94	60%	26	59%	0.005
Race	White	228	89%	125	80%	39	89%	0.032
	Black	29	11%	32	20%	5	11%	
Education		16.1	2.3	15.1	2.6	15.6	3.0	< 0.001
Systolic blood pressure		129.7	18.0	134.1	18.3	135.9	21.3	0.020
Diastolic blood pressure		69.8	10.4	71.1	9.2	71.7	9.7	0.292
BMI (kg/m^2)		27.6	5.6	27.5	5.1	25.8	4.1	0.097
Hypertension status	Present	171	67%	126	81%	35	80%	0.007
	Absent	83	33%	30	19%	9	20%	
Montreal Cognitive Assessment (MoCA)		26.4	2.4	22.0	3.3	16.8	4.8	< 0.001
Craft story		20.8	5.6	13.8	6.1	4.6	6.1	< 0.001
mPACC5 (z-score)		0.0	0.6	−1.3	0.8	−3.4	1.4	< 0.001
Global dementia scale		1.2	1.7	1.8	2.1	2.3	2.0	< 0.001
Clinical dementia rating scale		0.3	0.6	1.1	0.9	4.7	2.4	< 0.001
Carotid-femoral pulse wave velocity (m/s)		7.8	1.6	8.2	1.9	8.1	1.9	0.131

Abbreviations: BMI, body mass index; MRI, magnetic resonance imaging; PWV, pulse wave velocity; SD, standard deviation.
Notes: Hypertension defined as Stage 1, Stage 2 hypertension, or antihypertension medications. Modified Preclinical Alzheimer's Cognitive Composite (mPACC5) version FCSRT96 is reported. Sample restricted to participants with at least one of the five MRI measures reported plus PWV measurement and all three covariates (age, sex, race).

TABLE 2 Standardized cognitive test performance associated with vascular factors

	Carotid-femoral pulse wave velocity (cfPWV, m/s)			Systolic blood pressure (SBP, mmHg)		
Cognitive test	N	beta (SE)	*P*-value	N	beta (SE)	*P*-value
Global cognition (MoCA)	454	−0.066 (0.025)	0.009	449	−0.010 (0.002)	< 0.001
mPACC5	446	−0.101 (0.035)	0.004	441	−0.011 (0.003)	< 0.001
Memory domain	457	−0.006 (0.030)	0.834	452	−0.003 (0.003)	0.345
Executive domain	457	−0.041 (0.024)	0.097	452	−0.006 (0.002)	0.007
Language domain	456	−0.013 (0.022)	0.553	451	−0.005 (0.002)	0.026
Attention domain	457	−0.003 (0.027)	0.911	452	−0.003 (0.003)	0.173
Visuospatial domain	454	0.015 (0.028)	0.598	449	0.001 (0.003)	0.765

Notes: Unadjusted models of cognitive constructs that are normed for age, sex, race, and education and presented as z-scores.
Regression coefficients correspond to change in cognitive test performance corresponding to a one SD increase in PWV or SBP included in separate models.
Abbreviations: MoCA, Montreal Cognitive Assessment; mPACC5, Modified Preclinical Alzheimer's Cognitive Composite; PWV, pulse wave velocity; SBP, systolic blood pressure; SD, standard deviation; SE, standard error.

differences between cognitive adjudication groups in age, sex, education, SBP, body mass index, and the presence of cardiometabolic disorders. cfPWV was not significantly different among cognitive adjudication groups. The prevalence of hypertension was higher in MCI and dementia groups compared to cognitively normal participants. Body mass index was significantly lower, and SBP significantly higher, in participants with dementia compared to cognitively normal and MCI participants ($P < 0.01$). Higher cfPWV was significantly correlated with higher SBP ($r = 0.32$, $P < 0.001$).

3.2 | Cognitive function

Higher cfPWV and higher SBP were associated with worse normed performance on cognitive testing (Table 2). Higher cfPWV was associated with lower global cognitive performance ($P < 0.010$) and mPACC5 scores ($P = 0.004$). Higher cfPWV was also associated with lower performance in the domain of executive functioning ($P = 0.030$) but without significant associations to the memory, language, attention, and visuospatial domains. Similarly, higher SBP was associated with lower global cognitive performance ($P < 0.001$) and the mPACC5 ($P < 0.001$). Higher SBP was also negatively associated with performance in the domains of executive function ($P = 0.007$) and language ($P = 0.026$) without significant association with memory, attention, and visuospatial domains.

3.3 | MRI measures

Table 3 presents the multivariable regression models for the five primary MRI metrics of interest (FW, FA, WMHv, CBF) in the WM and CBF in GM. In adjusted models, higher cfPWV was associated with lower WM microstructure (higher FW; lower FA) and higher WMHv. SBP was associated with higher FW, but not with FA. SBP was associated with higher WMHv and lower WM and GM CBF.

When cfPWV and SBP were included in models together with further adjustment for hypertension treatment, higher cfPWV was significantly associated with higher FW independent of SBP and BP medication, and marginally associated with lower FA. SBP was also independently associated with higher FW, but not with FA or WMHv. Higher SBP was also associated with lower WM CBF, independent of PWV and treatment. Neither cfPWV nor SBP were significantly associated with differences in GM cortical thickness ($P > 0.05$, data not shown). We observed a significant interaction by *APOE* ε4 suggesting differential effects by *APOE* ε4 (*P*-interaction = 0.032). Among *APOE* ε4 carriers, PWV was associated with greater GM CBF ($\beta = 0.12$, standard error [SE] = 0.09) and among individuals without *APOE* ε4 allele, greater PWV is inversely associated ($\beta = -0.09$, SE = 0.05); however, PWV was not significantly associated with GM CBF in either group. cfPWV had stronger associations with FW, FA, and WMHv in men (*P* all < 0.05). SBP had stronger positive associations with WMHv in younger participants. No other interactions, including interactions with cognitive status or race, were detected at $P < 0.05$.

4 | DISCUSSION

In this sample of ADRC participants, greater arterial stiffness, measured by higher cfPWV, was associated with differences in WM microstructure (higher FW; lower FA) and brain macrostructure (higher WMHv). Similarly, SBP was also associated with differences in WM microstructure (higher FW) and brain macrostructure (higher WMHv; lower WM and GM CBF). Both cfPWV and SBP had negative associations with global and executive cognitive performance. SBP, but not cfPWV, had a significant association with worse performance in the language domain. We also observed differences among cognitive adjudication groups (normal cognition, MCI, dementia) in demographic data, SBP, hypertension, and cognitive performance.

These findings support and expand previous research, which has shown that higher PWV is associated with higher WMHv as well as decreased FA;[23,26] however, the relationship between PWV and WMHv was attenuated by adjustment for SBP and antihypertensive treatment. While very few studies have compared PWV to NODDI metrics of FW, our findings support these findings that higher PWV is

TABLE 3 Linear regression coefficients of vascular factors and brain MRI measures

		NODDI free water WM (n = 415)				Fractional anisotropy WM (n = 438)				White matter hyperintensity volume (n = 455)				Gray matter cerebral blood flow (n = 423)				White matter cerebral blood flow (n = 423)			
		N	beta	SE	*P*-value	N	beta	SE	*P*-value	N	beta	SE	*P*-value	N	beta	SE	*P*-value	N	beta	SE	*P*-value
cfPWV (m/s)	Model 1	415	0.205	0.046	<.001	438	−0.109	0.051	0.034	455	0.101	0.043	0.021	424	−0.062	0.047	0.194	423	0.026	0.052	0.616
	Model 2	410	0.183	0.047	<.001	433	−0.099	0.052	0.058	450	0.079	0.044	0.077	418	−0.040	0.048	0.410	418	0.053	0.053	0.317
SBP (mmHg)	Model 1	410	0.140	0.046	0.003	433	−0.095	0.049	0.053	450	0.102	0.041	0.013	418	−0.106	0.045	0.020	418	−0.107	0.050	0.032
	Model 2	410	0.093	0.046	0.045	433	−0.065	0.050	0.195	450	0.083	0.043	0.055	418	−0.087	0.046	0.062	418	−0.107	0.051	0.035

Notes: Model 1 adjusted for age, sex, race, and education. Model 2 adjusted for age, sex, race, education, and hypertension treatment, with SBP and cfPWV in the model together. Regression coefficients correspond to change in cognitive test performance corresponding to a one SD increase in PWV or SBP.

Abbreviations: cfPWV, carotid-femoral pulse wave velocity; NODDI, neurite orientation density and dispersion imaging; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; WM, white matter.

more strongly associated with microstructural integrity than SBP.[8,26] Our results show that higher cfPWV had a significant negative association with FA, but this relationship was attenuated by adjustment for SBP and antihypertensive treatment; additionally, the relationship between SBP and FA was not significant. Previous work has found FA to statistically mediate relationships between FW and WMH,[23] which indicates the potential predictive value of blood pressure control and specifically targeting arterial stiffness on maintaining WM microstructural integrity. Our results also show that SBP, but not cfPWV, was associated with lower CBF in both WM and GM. This is in contrast to previous research that has shown that higher PWV is associated with lower CBF,[10] and lower CBF is thought to provide regional information for areas of tissue at risk for WMH.[9] There also appear to be important differences in the relationships between PWV and global CBF by *APOE* ε4 that need to be addressed in future studies. SBP may be used to gauge general risk for WMH while PWV may have more specificity to the extent of disruption of WM microstructural measures. We observed that neither vascular measurement was associated with differences in temporal cortical thickness. Cortical thickness decreases generally and proportionally with age, with worse vascular health associated with thinner cortex.[44] Current research is inconclusive as to the exact effects of general loss of cortical thickness on brain function.[21,44]

Cognitive function depends greatly on regional variation in brain perfusion and integrity, as different aspects of cognition are focused in different brain regions. Generally, our results reflected current research in that higher PWV and higher SBP were both associated with worse global cognitive performance, a preclinical cognitive composite, and executive function. Interestingly SBP was more strongly associated with worse performance on the language domain, supporting most studies comparing blood pressure to linguistic performance.[45]

Arterial stiffness has been found to be higher in people with AD than in subjects with MCI or normal cognition.[26] While we did not observe significant differences in arterial stiffness across cognitive adjudication groups that were limited in size, we did see trends toward a difference between groups, with normal cognition having the lowest cfPWV average.

Limitations to this work should be considered in its interpretation. While 20% of our sample included individuals who self-reported as Black or African American, we were likely under-powered to detect effect modification by race. Further, this sample had a limited number of individuals with diabetes, as diabetes treatment was initially an exclusion criteria at recruitment. Within the first 2 years of recruitment, enrollment expanded to individuals with diabetes not treated with insulin. This study also focused on brain structural integrity and perfusion and did not include AD biomarkers or other measures of focal cerebral small vessel disease. Though there is a growing body of work supporting the concomitant development of subclinical vascular disorders, cerebral small vessel disease, and Aβ deposition in the brain,[15,46] those relationships were beyond the scope of this study. While our study included global measures of brain integrity, previous research has also examined specific brain areas including the corona radiata, corpus callosum, superior longitudinal fasciculus, and internal capsule. Abnormalities in these four regions are thought to precede

WMH development[26] and are thought to be especially susceptible to high blood pressure.[47] Future investigation may include defined structures, watershed regions, or the brain regions that may be affected earliest and most profoundly in age-related dementia.[37] Last, this study was limited by its cross-sectional nature, restricting inferences about causal and temporal relationships between risk factors and cerebrovascular integrity. Without longitudinal data, it is unclear whether increased arterial stiffness and blood pressure affect brain function directly or are one of several progressive or mediating[23] steps leading to decreased brain function. Future research should strive to include a more robust recruitment of different racial groups, men, and people with lower education.

In summary, we observe that elevated blood pressure and arterial stiffness are associated with abnormalities in WM microstructure and macrostructure. These findings reinforce the growing body of literature that suggests that blood pressure and arterial stiffness are biomarkers of cerebrovascular risk that may occur before the onset of symptoms. Altogether, these findings, supported by previous research, indicate that arterial stiffness could potentially be used as a target to prevent WM damage and associated cognitive impairment. Early and intensive treatment of elevated blood pressure can slow progression of WM disease[48] and prevent cognitive impairment.[49]

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CONFLICTS OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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