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Relations of arterial stiffness and endothelial function to brain aging in the community

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ABSTRACT

Objective: To determine the association of arterial stiffness and pressure pulsatility, which can damage small vessels in the brain, with vascular and Alzheimer-type brain aging.

Methods: Stroke- and dementia-free Framingham Offspring Study participants (n = 1,587, 61 ± 9 years, 45% male) underwent study of tonometric arterial stiffness and endothelial function (1998–2001) and brain MRI and cognition (1999–2002). We related carotid-femoral pulse wave velocity (CFPWV), mean arterial and central pulse pressure, and endothelial function to vascular brain aging by MRI (total cerebral brain volume [TCBV], white matter hyperintensity volume, silent cerebral infarcts) and vascular and Alzheimer-type cognitive aging (Trails B minus Trails A and logical memory-delayed recall, respectively).

Results: Higher CFPWV was associated with lower TCBV, greater white matter hyperintensity volume, and greater prevalence of silent cerebral infarcts (all $p < 0.05$). Each SD greater CFPWV was associated with lower TCBV equivalent to 1.2 years of brain aging. Mean arterial and central pulse pressure were associated with greater white matter hyperintensity volume ($p = 0.005$) and lower TCBV ($p = 0.02$), respectively, and worse verbal memory (both $p < 0.05$). Associations of tonometry variables with TCBV and white matter hyperintensity volume were stronger among those aged 65 years and older vs those younger than 65 years ($p < 0.10$ for interaction). Brachial artery endothelial function was unrelated to MRI measures (all $p > 0.05$).

Conclusions: Greater arterial stiffness and pressure pulsatility are associated with brain aging, MRI vascular insults, and memory deficits typically seen in Alzheimer dementia. Future investigations are warranted to evaluate the potential impact of prevention and treatment of unfavorable arterial hemodynamics on neurocognitive outcomes. *Neurology*® 2013;81:984–991

GLOSSARY

AGES = Age, Gene/Environment Susceptibility; **CFPWV** = carotid-femoral pulse wave velocity; **TCBV** = total cerebral brain volume; **Trails B-A** = Trail Making Test Part B minus Part A; **WMH** = white matter hyperintensity; **WMHV** = white matter hyperintensity volume.

Vascular remodeling associated with aging and cardiovascular disease risk factors leads to increased arterial stiffness and pressure pulsatility,[1,2] which transmits distally to damage the microcirculation,[3] resulting in cardiovascular events, including stroke.[4–7] Vascular injury may manifest as subclinical microinfarcts, white matter hyperintensities, or cerebral atrophy and may ultimately result in cognitive impairment, including Alzheimer-type dementia.[8,9] While an elderly sample demonstrated findings consistent with these hypotheses,[10] literature describing these relationships in nonhypertensive and community-based cohorts is sparse.

Flow-mediated dilation, the ability of the vasculature to adjust flow in response to endogenous or exogenous stimuli, provides another measure of vascular function distinct from arterial stiffness. Reduced flow-mediated dilation is associated with increased cardiovascular risk and is a surrogate for vascular dysfunction.[11,12] Studies in small samples have reported an association of

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impaired vascular function with subclinical markers of cerebral dysfunction including white matter hyperintensities[13] and cognitive decline.[14]

Thus, we hypothesized that in a middle-aged to older adult sample, greater arterial stiffness and pressure pulsatility and worse endothelial function would be associated with subclinical cerebrovascular damage, manifested as detectable structural brain MRI deficits and impaired cognition. We further hypothesized that the associations of tonometry variables with brain MRI measures would be greater in those of older ages. Lastly, we hypothesized that the inverse association of vascular dysfunction with cognition would be consistent for tests of vascular and Alzheimer-type brain aging. We examined associations of tonometry and brachial artery measures with subclinical neurologic disease consistent with brain aging in the community-based Framingham Heart Study.

METHODS

Study participants. The design of the Framingham Offspring Cohort Study has been detailed previously.[15] Of the 3,539 participants who attended Exam 7 (1998–2001), 2,293 participants had successful arterial tonometry measures; of these, 1,654 individuals had neurocognitive measures. Participants were excluded for prevalent dementia, stroke, or other neurologic conditions (e.g., multiple sclerosis, craniectomy, severe head injury, or brain tumor) that could affect the assessment of cognition and MRI brain volume (n = 67). Brachial artery measures were available in a subset of the sample (baseline diameter, n = 1,559; flow-mediated dilation, n = 1,496; baseline and hyperemic flow, n = 1,453). Of the participants with vascular function measures, 1,419 had brain MRI (exclusions: claustrophobia, contraindications, or declining MRI).

Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the Institutional Review Board at the Boston University Medical Center, and all participants gave written informed consent.

Arterial tonometry. ***Data acquisition.*** Applanation tonometry was acquired in the morning under fasting conditions. Supine brachial systolic and diastolic blood pressures were obtained using an oscillometric device. Simultaneous ECG and the pulse wave of the carotid, brachial, and femoral arteries were recorded using a commercially available tonometer (SPT-301; Millar Instruments, Houston, TX). Transit distance from the carotid to femoral arteries was assessed by body-surface measurements from the suprasternal notch to the carotid and femoral pulse recording sites. Tonometry and ECG data were digitized during the primary acquisition (1,000 Hz) and underwent analysis blinded to clinical data (Cardiovascular Engineering, Inc., Norwood, MA).

Tonometry data analysis. Tonometry waveforms were signal-averaged using the ECG R-wave as a fiducial point. Mean arterial pressure was determined by tonometry using the integrated mean of the signal-averaged brachial pressure waveform, which was calibrated using average systolic and diastolic cuff pressures. Diastolic and integrated mean brachial pressures were used to calibrate carotid pressure tracings.[16] Calibrated carotid pressure waveforms were used as a surrogate for central pulse pressure.[16] Carotid-femoral pulse wave velocity (CFPWV) was computed as the pulse wave transit distance divided by the transit time of the pulse wave from the carotid to femoral arteries using tonometry waveforms and body-surface measurements, with adjustment for parallel transmission of the arterial pulse wave in the brachiocephalic artery and aortic arch.[17]

Brachial artery flow-mediated dilation and reactive hyperemia were measured using high-resolution ultrasound (Toshiba SSH-140A, 7.5-MHz linear array transducer, Tustin, CA) to record images of the brachial artery at baseline and 1 minute after induction of reactive hyperemia by a 5-minute cuff occlusion at the forearm.[18] Images were measured offline (v.3.2.3.sp2, Brachial Analyzer, Medical Imaging Applications, Iowa City, IA). Doppler flow was assessed at baseline and for 15 seconds after cuff release using a carrier frequency of 3.75 MHz. Mean flow velocity at baseline and during reactive hyperemia was analyzed with correction for insonation angle using a semiautomated signal-averaging method.[18] All measures and analyses were performed blinded to clinical data.

Volumetric brain MRI outcomes. Details of brain MRI acquisition parameters, blinded image analysis, definition of brain volumes (indexed for cranial cavity size), and their descriptive statistics among all participants (n = 2,259) who underwent brain MRI have been published.[19,20] On a Siemens 1T or 1.5T scanner, 3-dimensional T1- and T2-weighted double spin-echo images were acquired in 4-mm contiguous slices (repetition time 2,420 milliseconds, echo time 1 = 20 milliseconds/echo time 2 = 90 milliseconds, echo train 8 milliseconds, field of view 22 cm, matrix 182 × 256 interpolated to 256 × 256 with one excitation). Total cerebral brain volume (TCBV) and white matter hyperintensity volume (WMHV) were computed as ratios with respect to total cranial volume to correct for differences in head size. WMHV was natural logarithmically transformed to normalize its skewed distribution. Prevalent silent cerebral infarcts were identified based on size >3 mm, vascular distribution, without mass effect, and hyperintense on T2- and proton density-weighted images. The interrater reliabilities ranged between 0.90 and 0.94 for total cranial volume, TCBV, and WMHV, and between 0.73 and 0.90 for silent cerebral infarcts. We evaluated 3 primary brain MRI measures: TCBV, an index of overall brain aging, and WMHV and silent cerebral infarcts, indices of vascular brain aging. All measurements were performed centrally (QUANTA 6.2, Sun Microsystems Ultra 5 workstation, Santa Clara, CA).

Neurocognitive outcomes. Using standard instructions, trained interviewers administered test batteries measuring a range of domain-specific outcomes.[21] Because we hypothesized an association between arterial hemodynamics and brain aging, we selected 2 tests a priori to represent a spectrum of neurocognitive function: logical memory-delayed recall, a marker of Alzheimer-type aging, and Trail Making Test Part B minus Part A (Trails B-A) score, an index of executive function and vascular brain aging. Trails B-A was logarithmically transformed to normalize the positively skewed distribution.

Covariates. We included the following Exam 7 covariates: diabetes, atrial fibrillation, ECG left ventricular hypertrophy, current smoking, antihypertensive medication, prevalent cardiovascular disease (coronary heart disease, congestive heart failure, intermittent claudication), presence of central obesity (sex-specific top quartile of waist-hip ratio), education, and depression (Center for Epidemiologic Studies Depression Scale), and plasma total and high-density lipoprotein cholesterol, triglycerides, and homocysteine (latter 2 logarithmically transformed). We further adjusted for *APOE* ε4 status

(ε4 allele carrier) and interval in years between Exam 7 and date of MRI or cognitive testing.

Statistical analysis. Central pulse pressure was logarithmically transformed to normalize the skewed distribution. CFPWV was inverse-transformed to reduce heteroscedasticity and multiplied by −1,000 to restore directionality and to convert the units to milliseconds/meter.

Separate analyses investigated relations of vascular measures with brain MRI and neurocognitive outcomes. We used 2 multivariable linear and logistic regression models to analyze continuous and categorical outcomes, respectively. Model 1 adjusted for age, sex, and mean arterial pressure, with the addition of education and depression scale as covariates for cognitive outcomes. Model 2 adjusted for variables included in model 1 with the addition of time interval between Exam 7 and MRI or neurocognitive testing, total and high-density lipoprotein cholesterol, log-triglycerides, log-homocysteine, plus indicators for diabetes, atrial fibrillation, smoking, antihypertensive treatment, prevalent cardiovascular disease, *APOE* ε4 genotype, and fourth quartile of waist-hip ratio.[22] Continuous outcomes were standardized (to mean 0, SD 1) to facilitate comparisons.

Secondary analyses examined effect modification by age younger than 65 years and 65 years and older of the relations between tonometry and brain MRI measures because we hypothesized that these associations may be stronger at older ages. Results for continuous outcomes are presented as the effect size ± standard error (on the brain MRI or neurocognitive measure) per SD unit increment in tonometry or endothelial function measure. For primary and interaction analyses, p values of <0.05 and <0.10, respectively, were considered significant. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Table 1 Characteristics of the Framingham Offspring Cohort[a]

Demographic and clinical characteristics of the sample (n = 1,587)	
Women, n (%)	873 (55)
Age, y	61 ± 9
Interval between tonometry and MRI or cognitive testing, y	0.7 ± 0.8
Systolic blood pressure, mm Hg	126 ± 19
Diastolic blood pressure, mm Hg	74 ± 10
Antihypertensive medication, n (%)	478 (30)
Diabetes mellitus, n (%)	159 (10)
Atrial fibrillation, n (%)	50 (3)
Current smoking, n (%)	195 (12)
Prevalent cardiovascular disease, n (%)	162 (10)
APOE ε4 genotype, n (%)	357 (23)
Plasma total homocysteine level, μmol/L, median (Q1, Q3)	7.6 (6.3, 9.3)
Waist/hip ratio, median (Q1, Q3)	0.95 (0.89, 1.00)
Education, n (%)	
No high school degree	54 (3)
High school	479 (30)
Some college	398 (25)
College degree	318 (20)
Postcollege	337 (21)
Center for Epidemiologic Studies Depression Scale score, median (Q1, Q3)	3.0 (1, 7)
Vascular function measures (n =1,587)[b]	
Carotid femoral pulse wave velocity, m/s, median (Q1, Q3)	9.0 (7.6, 11.0)
Mean arterial pressure, mm Hg	91 ± 12
Central pulse pressure, mm Hg, median (Q1, Q3)	47 (38, 59)
Baseline brachial artery diameter, mm	4.2 ± 0.9
Flow-mediated dilation, mm	0.1 ± 0.1
Flow-mediated dilation, %	2.9 ± 2.8
Baseline mean flow velocity, cm/s	8.1 ± 4.8
Hyperemic mean flow velocity, cm/s	52 ± 21
MRI measures (n = 1,419)	
Total brain cerebral volume, %	79 ± 3
White matter hyperintensity volume, %, median (Q1, Q3)	0.05 (0.03, 0.09)
Silent cerebral infarct, n (%)	142 (10)
Neurocognitive measures (n = 1,587)	
Logical memory-delayed recall, no. correct	10.7 ± 3.6
Trails B − Trails A, time to completion, min, median (Q1, Q3)	0.7 (1.4, 1.0)

Abbreviation: Q = quartile.
[a] Values presented as mean ± SD for continuous variables. Total cerebral brain volume and white matter hyperintensity volume are each expressed as %.
[b] Sample size reduced for measures of brachial artery function: flow-mediated dilation was available in n = 1,496, and baseline and hyperemic flow measures were available in n = 1,453.

RESULTS **Characteristics of study participants.** Table 1 shows the clinical and demographic characteristics and descriptive statistics for tonometric, brain MRI, and neurocognitive measures in the sample.

Relations of central aortic hemodynamic measurements to brain structure. The associations between aortic hemodynamic measurements and brain structure and function are presented in table 2. The decrease in mean TCBV associated with an SD increment in CFPWV was approximately equivalent to 1.2 years of brain aging, computed by the ratio of regression coefficient of CFPWV and age on TCBV. Greater CFPWV was also associated with WMHV ($p = 0.04$). Each SD higher CFPWV also conferred a 45% increased odds of silent cerebral infarcts in model 2 ($p = 0.009$). Each SD higher central pulse pressure was associated with lower TCBV ($p = 0.02$, model 2) but was not associated with WMHV or silent cerebral infarcts. Greater mean arterial pressure was associated with greater WMHV ($p = 0.005$, model 2). Mean arterial pressure was marginally associated with silent cerebral infarcts in the age- and sex-adjusted model ($p = 0.047$), which was attenuated with multivariable adjustment.

In secondary analyses, we observed effect modification by age in the associations of CFPWV and central pulse pressure with TCBV as well as CFPWV and mean arterial pressure with WMHV (figure). Whereas greater CFPWV was associated with lower TCBV in individuals younger than 65 years and also in those 65 years and older, the effect size was greater

Table 2 Association of arterial stiffness and pressure pulsatility with neurovascular and neurocognitive outcomes[a]

	TCBV, β ± SE	WMHV, β ± SE	Silent cerebral infarct, OR (95% CI)	Logical memory-delayed, β ± SE	Trails B-A, β ± SE
CFPWV					
Model 1	−0.12 ± 0.03[b]	0.05 ± 0.03	1.41 (1.09–1.83)[c]	−0.01 ± 0.03	−0.08 ± 0.03[d]
Model 2	−0.07 ± 0.03[d]	0.07 ± 0.04[d]	1.45 (1.10–1.90)[c]	0.01 ± 0.04	−0.07 ± 0.04
Central pulse pressure					
Model 1	−0.07 ± 0.03[c]	−0.01 ± 0.03	0.94 (0.76–1.17)	−0.07 ± 0.03[d]	−0.01 ± 0.03
Model 2	−0.06 ± 0.03[d]	0.002 ± 0.03	0.97 (0.60–1.56)	−0.07 ± 0.03[d]	−0.02 ± 0.03
Mean arterial pressure					
Model 1	0.02 ± 0.02	0.07 ± 0.02[c]	1.20 (1.00–1.42)[d]	−0.04 ± 0.02	0.02 ± 0.02
Model 2	0.03 ± 0.02	0.07 ± 0.03[c]	1.00 (0.99–1.02)	−0.05 ± 0.03[d]	0.02 ± 0.03

Abbreviations: CFPWV = carotid-femoral pulse wave velocity; CI = confidence interval; OR = odds ratio; SE = standard error; TCBV = total cerebral brain volume; Trails B-A = Trail Making Test Part B minus Part A; WMHV = white matter hyperintensity volume.
[a] TCBV and WMHV are expressed as % of intracranial volume. CFPWV is inverted and multiplied by −1,000; central pulse pressure, WMHV, and Trails B-A were log transformed. Effects are shown as standardized regression coefficients or OR per 1-SD increase in tonometric measure. Model 1: adjusted for age, sex, and mean arterial pressure (plus education and Center for Epidemiologic Studies Depression Scale [CES-D] score ≥16 for cognitive variables). Association of mean arterial pressure with neurovascular and neurocognitive outcomes was adjusted for age and sex (plus education and CES-D score ≥16 for cognitive variables). Model 2: model 1 and additionally adjusted for time to MRI/neurocognitive testing, diabetes mellitus, atrial fibrillation, current smoking, hypertensive therapy, prevalent cardiovascular disease, total cholesterol, high-density lipoprotein, log (triglycerides), *APOE* ε4 genotype, log (homocysteine), and the fourth quartile of waist/hip ratio.
[b] $p < 0.001$.
[c] $0.001 \leq p < 0.01$.
[d] $0.01 \leq p < 0.05$.

in the older group (figure, A). Similarly, there was a greater effect size in the association of central pulse pressure with TCBV among participants aged 65 years and older (figure, A). Finally, we noted stronger associations of both CFPWV and mean arterial pressure with WMHV in those 65 years and older compared with those younger than 65 years (figure, B).

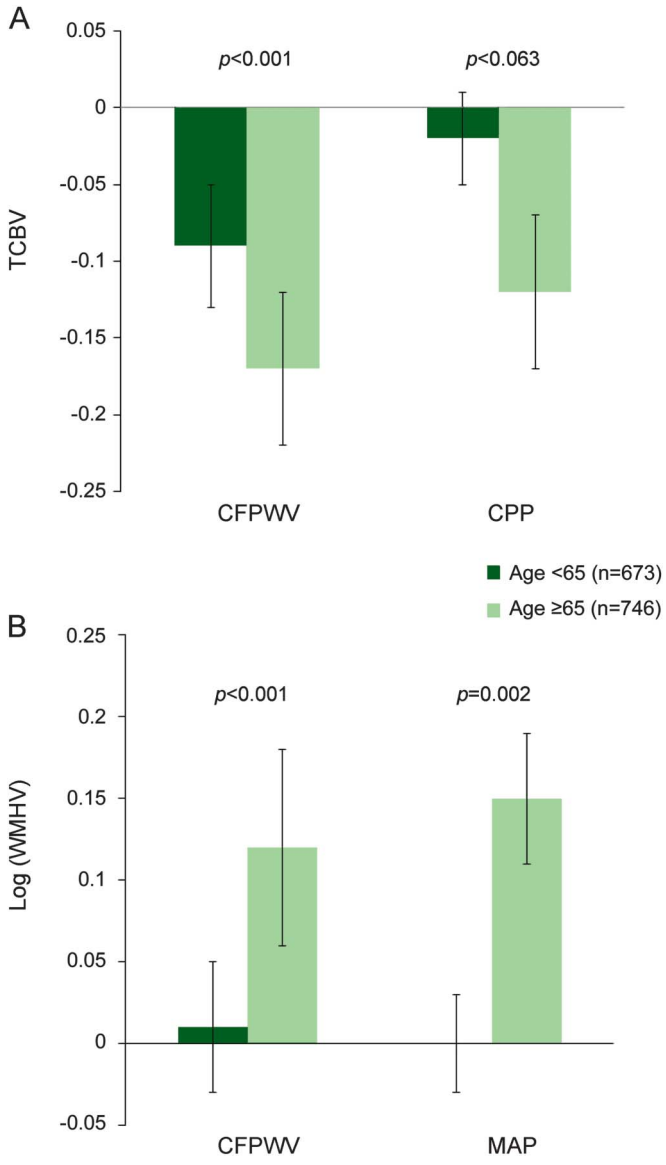
Relations of central aortic hemodynamics to cognitive function. CFPWV was not associated with logical memory-delayed or Trails B-A in our models (table 2). Greater central pulse pressure and mean arterial pressure were associated with lower logical memory-delayed scores ($p = 0.02$ and $p = 0.04$, respectively; model 2). Neither central pulse pressure nor mean arterial pressure was associated with Trails B-A.

Relations of brachial artery structure and function to brain structure and cognitive function. Baseline brachial artery diameter, flow velocity, hyperemic flow velocity, and flow-mediated dilation were not significantly associated with brain MRI measures (table e-1 on the *Neurology*® Web site at www.neurology.org). Baseline brachial artery diameter and flow velocity were positively associated with logical memory-delayed ($p = 0.04$ and $p = 0.02$, respectively; model 2). None of the measures of vascular endothelial function were associated with Trails B-A performance.

DISCUSSION In our community-based sample free of baseline stroke and dementia, we observed that measures of arterial stiffness and pressure pulsatility were associated with brain aging evaluated by brain MRI and cognitive testing. Higher CFPWV, an indicator of increased aortic stiffness, was associated with lower brain volumes, greater WMHV, and a higher prevalence of silent cerebral infarcts but was not related to measures of cognitive function. Greater central pulse pressure and mean arterial pressure were associated with lower brain volume and greater WMHV, respectively, and both were associated with lower scores on logical memory-delayed testing, which is associated with Alzheimer-type pathology. Finally, measures of brachial artery function were not associated with subclinical structural measures of aging or vascular damage detected by brain MRI. These data are consistent with our hypothesis that elevated central arterial stiffness and pulsatility lead to distal cerebral microvascular damage and brain atrophy, which manifests in subclinical cognitive dysfunction.

Mechanisms underlying the association between vascular function and neurocognitive decline. Increased aortic stiffness and elevated pulse pressure may stimulate vascular hypertrophy, remodeling, or rarefaction in the microcirculation, leading to increased resistance to mean flow and impaired microvascular reserve.[3,23] Endothelial function also is impaired by increased pressure pulsatility.[24] Increased arterial stiffness is associated with abnormal blood flow patterns, which increase transmission of pulsatile energy into the microcirculation, damaging the microcirculation. These abnormal

Figure Interaction of age on relations of tonometry and brain MRI measures



Effect sizes in the relations of tonometry measures with TCBV (A) and WMHV (B) were greater in those aged 65 years and older as compared with those younger than 65 years. Results displayed as mean β ± standard error SD change in TCBV or log (WMHV) for each SD greater continuous tonometric measure. The *p* values represent the significance level for an interaction term assessing effect modification by age in the full sample. CFPWV = carotid-femoral pulse wave velocity; CPP = central pulse pressure; MAP = mean arterial pressure; TCBV = total cerebral brain volume; WMHV = white matter hyperintensity volume.

physical forces in the arteries also trigger atherogenic, hypertrophic, and inflammatory responses, which may contribute to multisystem end-organ damage. In the brain, pathologic studies have demonstrated arteriosclerotic changes in small vessels in brain regions with white matter hyperintensity (WMH).[9,25]

Large-artery stiffening promotes blood pressure lability by increasing volume dependency of blood pressure and reducing baroreceptor sensitivity.[26] In individuals with stiff arteries, we speculate that resultant intermittent hypotension may lead to relative ischemia of the periventricular watershed zone, particularly when blood pressure lability is accompanied by blunted compensatory microvascular vasodilatory reserve. Although we did not assess blood pressure variability in our cohort, prior studies have shown that excessive systolic blood pressure variability between visits[27] and orthostatic hypotension at a single visit[28] are strongly associated with WMH severity and cognitive deficits. Furthermore, adverse hemodynamics may extend neurocognitive deficits above and beyond that conferred by nonvascular insults. In Alzheimer disease, growing evidence suggests that vascular disease accelerates manifestations of clinical dementia, and may even increase amyloid plaque deposition.[29,30]

Comparison with other studies. In hypertensive patients, CFPWV has been associated with the presence and extent of WMH and lacunar infarcts detected by brain MRI.[31–33] Consistent with its relations with structural changes of the brain, CFPWV also has been associated with delayed memory and reduced executive function.[10,34–36] The Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study found similar associations in a community-based sample including both treated hypertensive and nonhypertensive participants.[10] Consistent with AGES-Reykjavik, we observed associations of CFPWV with WMHV and silent cerebral infarcts and central pulse pressure with memory deficits. Similar to AGES, our study sample comprised both nonhypertensive as well as treated hypertensive participants, although the proportion of participants receiving treatment for hypertension was substantially lower in our sample (30% vs 60%). Our finding of a greater effect size of CFPWV with WMHV in those aged 65 years and older is consistent with the association seen in the AGES sample, in which the mean age of 75 years was a decade greater than that of the Framingham Offspring. The lack of association of CFPWV with cognitive function in our study may also be attributable to our sample's relatively younger mean age as compared with AGES. Finally, differences in the cognitive tests used for domain-specific assessment and variation in timing of tonometry, brain MRI, and cognitive testing may further account for differences between results.

The relations of endothelial function and brain structure and function have not been as well described in large populations. Overall, our findings do not suggest significant relations between brachial artery endothelial measures and brain structure or executive function. Higher mean baseline brachial artery diameter and flow were associated with better logical memory in our sample. However, our prior work has shown these brachial artery measures to be associated with adverse prognostic measures of cardiovascular health.[37–39] Given the biological implausibility and multiple testing, it is possible that

the association between baseline flow and logical memory was a chance finding. In smaller studies of middle-aged and older adults, flow-mediated dilation was inversely related to WMHV[13] and was associated with decreased performance on tests of memory and executive function.[14,40,41] However, we did not find any association between hyperemic flow or endothelium-dependent flow-mediated dilation with either brain MRI or cognitive measures.

Endothelial function in the brain has a key role in the regulation of blood flow through both secretion and response to vasoconstrictive and vasodilatory signals.[42] Local vascular disease in the brain is likely tightly coupled with brain structure and function,[43] but it is possible that endothelial function as measured in the forearm is too remote to correlate with our neurologic measures in the brain. Our relatively healthy sample may have contributed toward our null findings, but if replicated in other studies, our results may indicate that associations of arterial stiffness and brain abnormalities may not be mediated by impaired endothelial function assessed in the forearm.

Strengths and limitations. The strengths of our investigation are the community-based sample of middle-aged and older adults free of clinical stroke and dementia and the routine assessment of arterial hemodynamic and endothelial function measures. However, our study utilized single measures of brain MRI and cognitive testing. The cross-sectional, observational study design limits our ability to establish causal relations between arterial stiffness and brain aging measures. In addition, the relative health of our sample may have reduced the effect sizes and our sensitivity to detect associations between hemodynamic measures and neurologic outcomes. While some effect sizes may seem small, these were of a similar order of magnitude to that seen in AGES[10] and reflect substantial brain aging when examined comparatively to normal brain aging. Because the Framingham Offspring sample is largely white and of European ancestry, our results may not be generalizable to other ethnicities. Finally, because we did not account for multiple statistical testing, our results will need to be replicated in other cohorts. However, it is important to note that in these exploratory analyses, we evaluated relations of various moderately correlated hemodynamic measures with various correlated brain measures. Adjusting for multiple comparisons using a standard Bonferroni approach would be overly conservative and would result in an increased type II error rate in this setting.

CONCLUSIONS In this community-based sample of middle-aged and older individuals, measures of central arterial stiffness and adverse vascular hemodynamics were associated with both vascular and Alzheimer-type changes as assessed by brain MRI and neurocognitive testing. Our findings highlight the potential associations between central vascular hemodynamics and subclinical neurovascular disease at even younger ages than previously shown. Furthermore, our results add to the growing recognition that vascular insults potentially contribute to Alzheimer disease pathology and clinical manifestations. In light of the aging world population and the increased prevalence of arterial stiffness with greater age, efforts at primary and secondary prevention of vascular stiffness and remodeling may have significant public health implications via favorably influencing brain aging.

AUTHOR CONTRIBUTIONS

Dr. Tsao: analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content. Dr. Seshadri: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, study supervision. Dr. Beiser: analysis and interpretation of data, statistical analysis, critical revision of the manuscript for important intellectual content. Dr. Westwood: critical revision of the manuscript for important intellectual content. Dr. DeCarli: acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Au: critical revision of the manuscript for important intellectual content and administrative, technical, and material support. Ms. Himali: administrative, technical, and material support. Dr. Hamburg and Dr. Vita: acquisition of data. Dr. Levy: acquisition of data, critical revision of the manuscript for important intellectual content, and administrative, technical, and material support. Dr. Larson and Dr. Benjamin: critical revision of the manuscript for important intellectual content. Dr. Wolf: acquisition of data, critical revision of the manuscript for important intellectual content, and administrative, technical, and material support. Dr. Vasan: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Mitchell: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, study supervision.

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DISCLOSURE

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