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ASSOCIATION OF AORTIC STIFFNESS WITH COGNITION AND BRAIN AGING IN YOUNG AND MIDDLE-AGED ADULTS: THE FRAMINGHAM THIRD GENERATION COHORT STUDY

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Abstract

Aortic stiffness is associated with cognitive decline and cerebrovascular disease late in life, although these associations have not been examined in young adults. Understanding the effects of aortic stiffness on the brain at a young age is important both from a pathophysiological and public health perspective. The aim of the present study was to examine the cross-sectional associations of aortic stiffness with cognitive function and brain aging in the Framingham Heart Study Third Generation cohort (47% men, mean age = 46 years). Participants completed assessment of aortic stiffness (carotid-femoral pulse wave velocity), a neuropsychological test battery assessing multiple domains of cognitive performance and magnetic resonance imaging to examine subclinical markers of brain injury. In adjusted regression models, higher aortic stiffness was associated with poorer processing speed and executive function (Trail Making B-A; β±standard error = −0.08±0.03, $p < 0.01$), larger lateral ventricular volumes (β± standard error = 0.09±0.03, $p < 0.01$) and a greater burden of white matter hyperintensities (β± standard error = 0.09±0.03, $p < 0.001$). When stratifying by age, aortic stiffness was associated with lateral ventricular volume in young adults (30-45 years), whereas aortic stiffness was associated with white matter injury and cognition in midlife (45-65 years). In conclusion, aortic stiffness was associated with cognitive

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function and markers of subclinical brain injury in young to middle-aged adults. Prospective studies are needed to examine whether aortic stiffening in young adulthood is associated with vascular cognitive impairment later in life.

Keywords

Brain; cognition; cerebrovascular disorders; aortic stiffness; pulse wave velocity

Introduction

Aging is associated with a decline in cognitive ability.[1] While not all cognitive abilities decline substantially with age, those that do, such as processing speed[2] and reasoning skills,[1] hamper the ability of an individual to live life to its fullest.[3] Numerous efforts have been devoted to studying the causes of cognitive decline in old age, yet many cognitive functions appear to plateau or start declining as early as the second and third decades of life.[4]

A hallmark of arterial aging is the stiffening of the aorta;[5] which is a multifactorial process that begins early in life and progresses throughout the lifespan.[6] A highly elastic aorta serves to cushion pulsatile pressures created by left ventricular contraction thus delivering blood to peripheral organs in a near steady stream.[7] Stiffening of the aorta causes an increase in both aortic systolic and pulse pressure,[8] which are consequently less able to be dampened before travelling to peripheral organs.[7] Small blood vessels within the brain are particular vulnerable to damage as a result of high pressure and flow pulsatility, because the brain has a low vascular resistance and receives high flow throughout the cardiac cycle.[7, 9, 10]

Numerous studies have shown that aortic stiffness is associated with vascular brain injury and cognitive function in middle-aged or elderly subjects.[9, 11-18] However, aortic stiffening begins in early adulthood[19] and may be associated with cognition and subclinical evidence of cerebrovascular disease even in young adults. The aim of the present study was to examine the cross-sectional association of aortic stiffness with cognitive function and markers of subclinical brain injury in participants of the Framingham Heart Study Third Generation cohort, who are predominantly young to middle-age. As aortic stiffness increases around the same time many cognitive functions peak, we hypothesised that higher aortic stiffness would be associated with poorer cognitive performance and a greater burden of subclinical cerebrovascular disease on magnetic resonance imaging (MRI).

Methods

Participants

The Framingham Heart Study commenced in 1948 in Framingham, Massachusetts with the recruitment of the Original cohort.[20] An Offspring cohort was created in 1971[21] and a Third Generation cohort (grandchildren of the Original Cohort participants and children of the Offspring cohort participants) in 2002.[22] Upon enrolment, the Third Generation cohort included 4095 men and women, of whom 3411 returned for the second examination cycle conducted between 2008 and 2011. Among the participants who attended exam 2, 3218 had aortic stiffness measured and, of these, 3207 were free from stroke, dementia and other

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neurological conditions such as multiple sclerosis and severe head trauma and comprise our study sample. Of these, 3136 participants completed the Victoria Stroop task and 2192 participants completed all neuropsychological assessments. Of those with complete neuropsychological data, 1995 also had a brain MRI. With the exception of the Victoria Stroop task, which was performed during the second exam visit, neuropsychological assessment and brain MRI were performed an average of 1.7 years (standard deviation [SD] = 0.9) from the second examination cycle. All subjects provided written informed consent and the study procedures were approved by the Institutional Review Board at Boston University School of Medicine. All procedures were in accordance with institutional guidelines.

Applanation tonometry

Aortic stiffness was measured as carotid-femoral pulse wave velocity (CFPWV), the gold-standard non-invasive technique.[23] Measurements were performed in the morning with the participant fasted. Firstly, brachial blood pressures were obtained with an auscultatory device after the participant rested supine for approximately 5 minutes. Applanation of the brachial, radial, femoral and carotid arteries were then performed using a custom available tonometer (Cardiovascular Engineering, Inc., Norwood, Massachusetts) with simultaneous electrocardiogram (ECG) used to synchronize tonometry signals to the ECG R wave for the purpose of signal averaging. Path length for CFPWV was calculated along the body-surface by subtracting the distance between the carotid measurement site and suprasternal notch from the distance between the suprasternal notch and femoral measurement site. This method of subtraction adjusts for parallel transmission of the arterial pulse wave in the aortic arch and brachiocephalic artery. [8] The data were digitized and analysed blind to clinical information (Cardiovascular Engineering, Inc., Norwood, Massachusetts). CFPWV was calculated as the path length divided by the transit time of the pulse wave from the carotid to femoral sites. Mean arterial pressure (MAP) was calculated as the mean of the signal-averaged brachial pressure waveform, which was calibrated with systolic and diastolic cuff pressures. Brachial pulse pressure was calculated as systolic minus diastolic pressure.

Neuropsychological testing

Neuropsychological testing was performed by trained neuropsychologists. We included tests of Trail Making A and B as well as the Victoria Stroop interference task (processing speed and executive function), Logical Memory delayed (verbal memory), Visual Reproductions delayed (visual memory), the Hooper Visual Organization Test (visuo-perceptual skills) and Digits Span Forwards and Backwards (working memory). These tests were chosen because they are well-validated, widely used and performance is known to peak and then decrease beginning from the second or third decades of life. Our neuropsychological battery examines numerous broad cognitive domains as defined by the Cattell-Horn-Carroll model - one of the most widely accepted models of human cognitive ability[24] - including processing speed (and the neuropsychological concept of executive function), visual processing, short-term memory and long term storage and retrieval. Expanded details of the neuropsychological tests can be seen in Table S1 (please see http://hyper.ahajournals.org). All tasks were treated such that higher scores indicate superior performance, either in the form of more correct responses or faster task completion (Table S1).

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Structural MRI measures

Total brain volume (TBV), white matter hyperintensity volume (WMHV), lacune of presumed vascular origin (lacunes hereafter) and lateral ventricular volume were all evaluated using a 1.5-Tesla Siemens Avanto scanner. We used 3-dimensional T1-weighted coronal spoiled gradient-recalled echo (SPGR) acquisition and fluid attenuated inversion recovery (FLAIR) sequences. In order to correct for differences in head size, TBV, WMHV and lateral ventricular volume were expressed relative to total cranial volume on FLAIR. The methods for segmentation and quantification of brain volumes have been described previously.[25-27] Central cerebrospinal fluid spaces were analysed to calculate lateral ventricular volumes, excluding the temporal horn. The presence of lacunes was determined in accordance with the standards for reporting vascular changes on neuroimaging criteria.[28] All scans were read blind to subject identifying and clinical information.

Statistical analysis

Our primary analysis involved examining the associations of CFPWV with each cognitive and MRI based outcome in the whole sample. Secondary analysis involved examining the same associations, but separately for young (30 to < 45 years) and middle-aged (45 to < 65 years) participants. The purpose of this analysis was to investigate the earliest ages at which aortic stiffness is associated with cognitive performance and subclinical brain injury.

All analyses were performed using SAS software (SAS Institute, Cary, N.C.). To reduce heteroscedasticity, values of CFPWV were inverse transformed (−1000/CFPWV), meaning that CFPWV essentially became the square root of the average dispensability. Values were then multiplied by −1 to restore directionality (higher values indicate stiffer arteries). Values of WMHV were log transformed to normalize the distribution. All continuous outcome measures were transformed to a standard normal distribution. Associations between aortic stiffness and the outcome measures were performed using linear or logistic regressions. Regressions were performed according to two adjusted models. Model 1 adjusted for age, sex and time to neuropsychological testing or MRI (as well as education for neuropsychological outcomes). Model 2 included additional adjustment for prevalent diabetes, atrial fibrillation, current smoking, prevalent cardiovascular disease, total cholesterol, high density lipoprotein cholesterol, depressive symptoms (Center for Epidemiologic Studies Depression Scale [CES-D] score ≥16), the fourth quartile of waist to hip ratio, treatment for hypertension and MAP. All results were considered statistically significant if $p < 0.05$.

Results

The sample demographics are displayed in Table 1. The mean age of the study sample was 46 years and the median CFPWV was 6.8 meters/second. Only 2 percent of the sample had clinical cardiovascular disease. The baseline characteristics of the outcome measures are displayed in Table 2.

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Aortic stiffness and cognitive function

Across the whole sample, higher aortic stiffness was associated with worse performance on tests of Trails B, Trails B-A and Visual Reproductions delayed (in model 1; Table 3), indicating worse processing speed, executive function and visual memory (please see Table S1, http://hyper.ahajournals.org for details on the neuropsychological tests). In the fully adjusted model, aortic stiffness remained a predictor of Trails B-A while the associations with Trails B and Visual Reproductions failed to reach statistical significance (Table 3). Analysis by age subgroups revealed that aortic stiffness was associated with poorer performance on Trails B and Trails B-A in middle-aged but not young adults. Aortic stiffness was not associated with performance on any other cognitive tasks in this young sample.

Aortic stiffness and MRI

Higher aortic stiffness was associated with larger lateral ventricular volumes and WMHV (Table 4). Analysis by age subgroups indicated that the association between aortic stiffness and lateral ventricular volume was evident in young adulthood whereas the association with WMHV was only evident in midlife. Aortic stiffness was not associated with TBV or lacunes.

Post-Hoc Analysis

To investigate whether the imaging and neuropsychological findings were congruent in the middle-aged sample, we performed separate linear regression analyses with WMHV as the predictor and Trails B and Trails B-A as the outcomes. These analysis were adjusted for the covariates outlined in model 1. Results revealed that higher WMHV was associated with poorer performance on Trails B ($\beta \pm$standard error [SE] = -0.07 ± 0.03, $p < 0.05$) and Trails B-A ($\beta \pm SE = -0.06 \pm 0.03$, $p < 0.01$).

We also repeated the cognitive and MRI analyses with brachial pulse pressure as the exposure instead of CFPWV (please see Tables S2-3, http://hyper.ahajournals.org). The aim was to explore if brachial pulse pressure, a surrogate marker of aortic stiffness, was comparable to CFPWV in predicting the neurological outcomes. Brachial pulse pressure was not associated with any of the MRI outcomes but was associated with digit span and visual reproductions. Specifically, higher brachial pulse pressure was associated with poorer digit span in both the whole sample and in younger adults (in model 1). Higher brachial pulse pressure was also associated with better performance on the visual reproductions task in the whole sample (model 2) and in young adults (models 1 and 2). Post-hoc analyses were not adjusted for multiple comparisons and should be interpreted with caution.

Discussion

Aortic stiffness is associated with asymptomatic target organ damage, particularly in high flow organs such as the brain. [23, 29, 30] Whereas most studies of brain structure and function have focused on elderly cohorts, the present study examined the association between aortic stiffness and the earliest signs of brain aging in young adults of the Framingham Heart Study. We found that aortic stiffness, measured as CFPWV, was associated with a vascular

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pattern of subclinical brain injury, including deficits in processing speed and executive function as well as larger lateral ventricular volumes and WMHVs. Analysis stratified by age revealed that aortic stiffness was associated with subtle brain injury in young adults, although cognitive deficits were only evident in midlife.

The Framingham Heart Study previously reported that, in older adults (mean age of 62 years), aortic stiffness was associated with TBV, WMHV and covert brain infarcts.[11] Similarly, the Age, Gene/Environment Susceptibility (AGES) study (mean age of 75-76 years) demonstrated that aortic stiffness was also associated with covert brain infarcts and the burden of white matter hyperintensities (WMHs).[9] Results are relatively consistent across studies involving mostly elderly cohorts, with systematic reviews and meta-analyses demonstrating that aortic stiffness is associated with markers of small vessel disease[31] and subtle cognitive decline.[32] The present study extends these findings by demonstrating that high aortic stiffness is associated with white matter injury and lower cognitive function in midlife, and with a single marker of cortical atrophy in young adults. In our cross-sectional study, CFPWV was a better predictor of brain aging as compared to brachial pulse pressure. However, cross-sectional and longitudinal findings may vary given that previous cohort studies have found both pulse pressure and CFPWV to predict cognitive decline from middle-age onwards.[12]

WMHs are related to age and vascular risk factors with higher burdens suggestive of small vessel disease.[28, 33] WMHs are an uncommon finding in young individuals,[34] reflecting an end-stage process of white matter injury. [35] That is to say that more subtle white matter damage may precede the emergence of WMHs on FLAIR imaging, meaning that WMHs may lack sensitivity to brain injury in young adults. Lateral ventricular volume provides an indication of central brain atrophy and increases with age in a quadratic fashion.[36] The association between lateral ventricular volumes and CFPWV may also be due to ventricular enlargement given that the arterial pulse wave contributes to the flow and clearance of cerebrospinal fluid along perivascular spaces.[37-39] WMHV was related to poorer performance on the Trail Making test, indicating poorer executive function and processing speed, both in the present study and in past research.[40] Thus, the present cognitive and MRI results are congruent.

An unexplained finding of the current study was that, among those in midlife, the association between aortic stiffness and lateral ventricular volume failed to reach statistical significance in the fully adjusted model. Although the reasons for this are unclear, certain vascular risk factors are known to have an age-dependent association with neurological and neuropsychological outcomes.[41] It is possible that aortic stiffness was not associated with lateral ventricular volume in midlife because other vascular risk factors (adjusted for in model 2) better explained the variance in lateral ventricular volume. In contrast, aortic stiffness may have been more strongly associated with lateral ventricular volume in young adults, where the presence of competing vascular risk factors was lower. These explanations are speculative and other cohort studies are required to replicate and extend our findings to provide clarity on the present results.

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Strengths of the current study include the large and well characterized sample, the detailed neuropsychological assessment battery and the use of MRI to examine multiple markers of subclinical brain injury. Limitations of the study include the observational nature of the study, which precluded the inference of causality; the overwhelmingly white Caucasian sample, which restricts generalizability of the results to other races and ethnic groups; the fact that neuropsychological assessment was only performed at one occasion, preventing examination of how aortic stiffness relates to cognitive decline; and, as we did not adjust for multiple comparisons, we cannot rule out the presence of some chance associations.

Perspectives

Vascular disease is a significant contributor to cognitive impairment and dementia later in life.[42] It is likely that the degree of cognitive impairment and cerebrovascular insult depends on the length of exposure to vascular risk factors, with clinically silent cerebrovascular injury accumulating in an insidious fashion.[43] We demonstrate that aortic stiffness is associated with a single marker of cortical atrophy in young adults and that aortic stiffness is associated with white matter injury and cognitive function in midlife. Prospective studies are needed to extend our findings to evaluate the temporal associations between aortic stiffening, cerebral small vessel disease and cognitive decline, starting from an early age. Assuming causality between high aortic stiffness and lowered cognitive function, the appropriate management of cardiovascular disease risk factors may help limit aortic stiffening, potentially protecting against the development of small vessel disease and cognitive impairment later in life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

- What is New?

  Studies examining the association of aortic stiffness with cognition have focused on middle-aged to elderly cohorts. This study addresses the important need to understand whether aortic stiffness is associated with evidence of cognitive deficits and subclinical brain injury in young adults.

- What is relevant?

  Aortic stiffness is a hallmark of arterial aging and is associated with increases in central systolic and pulse pressure. Aortic stiffening increases pressure and flow pulsatility in the cerebrovasculature and is a marker for asymptomatic target organ damage.

- Summary

  Aortic stiffness was associated with central brain atrophy in young adulthood, and with white matter injury and cognitive performance in midlife.

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Table 1

Sample characteristics.

	Whole sample (N= 3207)	Men (N= 1505)	Women (n=1702)
Clinical characteristics			
Age, y	46 (9)	47 (9)	46 (9)
Education, n (%)			
No HS degree	23 (1)	18 (1)	5 (0)
HS degree	460 (14)	243 (16)	217 (13)
Some college	1001 (31)	448 (30)	553 (33)
College graduate	1714 (54)	794 (53)	920 (54)
Waist/Hip ratio	0.91 (0.08)	0.97 (0.06)	0.87 (0.07)
HTN treatment, n (%)	564 (18)	319 (21)	245 (14)
Total cholesterol, mg/dL	187 (34)	186 (35)	187 (34)
HDL cholesterol, mg/dL	59.7 (17.7)	51.0 (13.8)	67.4 (17.3)
Diabetes mellitus, n (%)	147 (5)	90 (6)	57 (3)
Atrial Fibrillation, n (%)	31 (1)	24 (2)	7 (0)
Prevalent CVD, n (%)	58 (2)	40 (3)	18 (1)
Current smoker, n (%)	322 (10)	166 (11)	156 (9)
Depression*, n (%)	292 (9)	119 (8)	173 (10)
Time from exam to MRI/NP, y	1.7 (0.9)	1.7 (1.0)	1.6 (0.9)
Hemodynamic measures			
SBP, mm Hg	116 (14)	121 (12)	112 (14)
DBP, mm Hg	74 (9)	77 (9)	72 (9)
MAP, mm Hg	87 (11)	89 (10)	85 (11)
CFPWV, m/s, median (Q1, Q3)	6.8 (6.1, 7.7)	7.2 (6.5, 8.1)	6.5 (5.9, 7.3)

Mean (SD) reported unless specified otherwise. CFPWV = carotid femoral-pulse wave velocity; CVD = cardiovascular disease; DBP = diastolic blood pressure; HDL = high density lipoprotein; HS = high school; HTN = hypertension; MAP = mean arterial pressure; MRI = magnetic resonance imaging; NP = neuropsychological assessment; Q= quartile; SBP = systolic blood pressure.

* Depressive symptoms based on scores ≥ 16 on the Center for Epidemiologic Studies on Depression Scale-Revised.

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Table 2

Characteristics of the outcome measures.

Measure	Whole sample	Men	Women
Neuropsychological Outcomes			
Processing Speed/Executive Function			
Trails A, median (Q1, Q3)	0.38 (0.32, 0.47)	0.40 (0.33, 0.48)	0.38 (0.32, 0.47)
Trails B, median (Q1, Q3)	0.93 (0.75, 1.17)	0.97 (0.78, 1.25)	0.90 (0.73, 1.12)
Trials B-A, median (Q1, Q3)	0.53 (0.38, 0.72)	0.57 (0.40, 0.78)	0.52 (0.37, 0.67)
Stroop interference	197.6 (57.0)	195.2 (54.6)	199.6 (58.8)
Long Term Storage and Retrieval			
Logical memory delayed	11.57 (3.76)	10.74 (3.65)	12.31 (3.71)
Visual Processing			
Visual reproductions delayed	8.90 (2.61)	8.98 (2.62)	8.82 (2.59)
Hooper VOT, median (Q1, Q3)	27.00 (25.50, 28.00)	27.00 (25.50, 28.50)	26.50 (25.50, 28.00)
Working Memory			
Digit span forward	6.90 (1.26)	7.01 (1.26)	6.80 (1.26)
Digit span backwards	5.14 (1.30)	5.20 (1.35)	5.10 (1.26)
MRI outcomes			
TBV, %	88.58 (2.64)	88.95 (2.62)	88.26 (2.63)
Lateral ventricular volume, %	1.16 (0.78)	1.26 (0.83)	1.07 (0.73)
Lacunes, n (%)	63 (3.2)	32 (3.4)	31 (2.9)
WMHV, %, median (Q1, Q3)	0.0003 (0.0002, 0.0007)	0.0003 (0.0002, 0.0006)	0.0003 (0.0002, 0.0007)

Notes. Data are displayed as mean (SD), unless specified otherwise. Q = quartile; TBV = total brain volume; VOT = visual organization test; WMHV = white matter hyperintensity volume.

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Table 3

Association of aortic stiffness with cognitive outcomes

	Whole sample		30 to < 45 years		45 to < 65 years	
Outcomes	**1**	**2**	**1**	**2**	**1**	**2**
n[§]	2182	2168	820	811	1260	1255
Processing Speed/Executive Function						
Trails A	−0.03±0.03	−0.01±0.03	−0.03±0.05	−0.01±0.05	−0.03±0.03	0.01±0.04
Trails B	**−0.07±0.03**[†]	−0.06±0.03	0.02±0.04	0.04±0.05	**−0.11±0.03**[‡]	**−0.10±0.04**[‡]
Trails B-A	**−0.08±0.03**[†]	**−0.08±0.03**[†]	0.04±0.04	0.05±0.05	**−0.14±0.04**[‡]	**−0.15±0.04**[‡]
Stroop Interference	−0.02±0.02	−0.05±0.03	−0.05±0.03	−0.04±0.04	−0.004±0.03	−0.06±0.04
Visual Processing						
Visual reproductions delayed	**−0.06±0.03**[*]	−0.02±0.03	−0.06±0.04	−0.07±0.05	−0.07±0.03	0.01±0.04
Hooper VOT	0.01±0.03	0.02±0.03	−0.04±0.04	−0.06±0.05	0.04±0.03	0.07±0.04
Short-term Memory						
Digit span forwards	−0.02±0.03	0.01±0.03	−0.003±0.04	0.02±0.05	−0.03±0.04	0.005±0.04
Digit span backwards	0.02±0.03	0.04±0.03	0.03±0.05	0.07±0.05	0.02±0.03	0.03±0.04
Long-Term Storage and Retrieval						
Logical memory delayed	−0.0004±0.03	−0.0004±0.03	0.002±0.04	−0.02±0.05	0.001±0.03	0.01±0.04

Notes: Data are displayed as estimated β±SE. Model 1 adjusts for age, time to neuropsychological assessment, sex and education. Model 2 includes additional adjustment for diabetes, atrial fibrillation, smoking, prevalent cardiovascular disease, total cholesterol, HDL cholesterol, depressive symptoms, waist/hip ratio, treatment for hypertension and mean arterial pressure. VOT = visual organization test.

[*] $p < 0.05$

[†] $p < 0.01$

[‡] $p < 0.001$

[§] Sample sizes for Stroop were n = 3127/3106 (whole sample, model 1/2), n = 1149/1138 (young adults, model 1/2) and n = 1825/1816 (middle-aged adults, models 1/2).

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Table 4

Association of aortic stiffness with markers of subclinical brain injury on magnetic resonance imaging.

	Whole sample		30 to < 45 years		45 to < 65 years	
Model	**1**	**2**	**1**	**2**	**1**	**2**
n	1995	1985	766	759	1132	1129
TBV	−0.05±0.03	−0.04±0.03	−0.08±0.05	−0.08±0.05	−0.04±0.03	−0.004±0.04
LVV	**0.09±0.03**‡	**0.09±0.03**†	**0.09±0.03**†	**0.09±0.04***	**0.09±0.04***	0.08±0.05
WMHV	**0.11±0.02**‡	**0.09±0.03**‡	0.04±0.04	0.01±0.05	**0.14±0.03**‡	**0.12±0.04**†
Lacunes	0.97 (0.70, 1.33)	0.95 (0.66, 1.38)	0.98 (0.51, 1.90)	1.03 (0.50, 2.15)	0.93 (0.63, 1.36)	0.90 (0.57, 1.41)

Notes. Data are displayed as estimated β±SE, except for lacunes, in which data are OR (95% CI). Model 1 adjusts for age, sex and time to MRI. Model 2 includes additional adjustment for diabetes, atrial fibrillation, smoking, prevalent cardiovascular disease, total cholesterol, HDL cholesterol, depressive symptoms, waist to hip ratio, treatment for hypertension and mean arterial pressure. LVV = lateral ventricular volume; TBV = total brain volume; WMHV = white matter hyperintensity volume.

* $p < 0.05$

† $p \leq 0.01$

‡ $p \leq 0.001$.