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ORIGINAL ARTICLE

Effects of Carotid Artery Stiffness on Cerebral Small-Vessel Disease and Cognition

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BACKGROUND: Carotid artery stiffness is associated with cognitive impairment and dementia, but the underlying mechanisms remain unknown. We examined the associations of carotid artery stiffness with cerebral small-vessel disease markers, cognition, and dementia subtypes in a memory clinic cohort.

METHODS AND RESULTS: A total of 272 participants underwent carotid ultrasonography, 3 Tesla brain magnetic resonance imaging, and neuropsychological assessment. Carotid ultrasonography was used to assess β-index, pressure-strain elastic modulus, and pulse-wave velocity-β. Brain magnetic resonance images were graded for cerebral small-vessel disease markers, including white matter hyperintensities, lacunes, and cerebral microbleeds. Participants were classified as having no cognitive impairment, cognitive impairment and no dementia, or dementia subtyped as Alzheimer disease and vascular dementia. Cognition was assessed using National Institute of Neurological Disorders and Stroke–Canadian Stroke Network harmonization battery. After adjusting for age, sex, cardiovascular risk factors, and diseases, multivariable models showed that β-index (β=0.69; P=0.002), elastic modulus (β=0.78; P<0.001), and pulse-wave velocity-β (β=0.80; P<0.001) were associated with white matter hyperintensities, and elastic modulus (odds ratio [OR], 1.39 [95% CI, 1.04–1.85]) and pulse-wave velocity-β (OR, 1.47 [95% CI, 1.10–1.98]) were independently associated with lacunes. Similarly, β-index (OR, 2.04 [95% CI, 1.14–4.13]), elastic modulus (OR, 2.22 [95% CI, 1.25–4.42]), and pulse-wave velocity-β (OR, 2.50 [95% CI, 1.36–5.18]) were independently associated with vascular dementia. Carotid stiffness measures were independently associated with worse performance in global cognition, visuomotor speed, visuospatial function, and executive function. These associations became largely nonsignificant after further adjusting for cerebral small-vessel disease markers.

CONCLUSIONS: In memory clinic patients, carotid artery stiffness was associated with white matter hyperintensities and lacunes, impairment in global and domain-specific cognition, and causative subtypes of dementia, particularly vascular. The effects of carotid stiffness on cognition were not independent of, and were partially mediated by, cerebral small-vessel disease.

Key Words: Alzheimer disease ■ carotid artery stiffness ■ cerebral small-vessel disease ■ cognition ■ vascular dementia

Conduit arterial stiffening leads to elevated systolic blood pressure, pulse pressure, left ventricular hypertrophy, as well as increased risk for cardiovascular diseases (CVDs), such as myocardial infarction, heart failure, and stroke.[1] Stiffening also affects the elastic common carotid artery, increasing its resistance to deformation by systolic blood pressure.[2] Contributors to vascular stiffness include carotid atherosclerosis, often manifested subclinically by carotid intima-media thickening and plaque formation.[3,4]

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CLINICAL PERSPECTIVE

What Is New?

- Our study demonstrated that increased carotid artery stiffness, derived by using central aortic pressures, was associated with cerebral small-vessel disease markers, vascular dementia, and cognition.
- Cerebral small-vessel disease partially mediates the detrimental effects of carotid stiffening on cognition.

What Are the Clinical Implications?

- Increased carotid artery stiffness may help identify patients with, or at risk for developing, cerebral small-vessel disease, cognitive impairment, and dementia, so that timely interventions and preventive strategies can be effectively administered.

Nonstandard Abbreviations and Acronyms

CIND	cognitive impairment no dementia
CSVD	cerebral small-vessel disease
Ep	elastic modulus
NCI	no cognitive impairment
PWV	pulse-wave velocity
VaD	vascular dementia
WMH	white matter hyperintensity

Carotid artery stiffness has been found to be associated with incident stroke independent of CVD risk factors and aortic stiffness assessed by carotid-femoral pulse wave velocity (PWV). Moreover, carotid stiffness modestly improved stroke risk prediction beyond Framingham stroke risk score factors and PWV, thus highlighting the importance of carotid stiffness in the pathogenesis of stroke.[5] Carotid artery stiffness is also associated with other cerebrovascular outcomes, such as cognitive impairment and dementia.[6–8] Although the mechanisms underlying this association are not clearly understood, and difficult to disentangle from shared CVD risks, it has been suggested that increased carotid artery stiffness leads to higher pulsatile pressure and flow load on the brain, which can disrupt cerebral microcirculation.[9,10] This increased pulsatile load penetrates deeply and damages the low impedance microvascular bed, where vascular resistance and protection from pulsatile forces are lower.[11–13] Such cerebral microvascular damage can manifest as cerebral small-vessel disease (CSVD), which is visible on brain magnetic resonance imaging (MRI) scans as white matter hyperintensities (WMHs), lacunar infarcts, and cerebral microbleeds.[6,14,15] These brain markers of CSVD are also known to be associated with dementia, cognitive impairment, as well as cognitive decline during follow-up.[16–18]

In our community-based study, carotid artery stiffness was found to be associated with impairment in global cognition in nondemented older adults without CVDs, but the associations with specific cognitive domains varied, with only executive function reaching significant association.[7] Other studies have also reported varying associations with executive function, processing speed, and episodic memory.[14,19,20] Nonetheless, there is little evidence to substantiate either a direct or an indirect relationship between carotid artery stiffness and cognition, as their relationship has not been examined in the presence of CSVD. If higher pulsatile pressure and flow load engendered by carotid artery stiffening damage the cerebral microcirculation, which are subsequently manifested by CSVD markers that are associated with cognition, then there should be an indirect relationship between carotid artery stiffness and cognition. In other words, the relationship between carotid artery stiffness and cognition should be attenuated in the presence of CSVD. To ascertain the mechanistic role of carotid artery stiffness in cognition, the present study aims to determine the association of carotid artery stiffness with CSVD markers, cognitive impairment, and causative subtypes of dementia, as well as with cognitive performance in a memory clinic population. We hypothesize that carotid artery stiffness is associated not only with worse cognitive performance, but also with CSVD markers on neuroimaging, cognitive impairment, and vascular dementia. In addition, we hypothesize that CSVD mediates the association between carotid artery stiffness and cognition.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Sample

This study was conducted as part of an ongoing memory clinic–based study, which recruits participants from the National University Hospital, Singapore. The following diagnostic categories at baseline were considered eligible for inclusion in this study: no cognitive impairment (NCI), cognitive impairment no dementia (CIND), and dementia. All participants underwent comprehensive evaluation, including physical, medical, and

neuropsychological assessments along with 3T brain MRI. Between August 2015 and February 2020, 272 participants were enrolled in a cardiovascular substudy, where they additionally had a 12-lead ECG and vascular imaging. The mean duration between (a) MRI scans and neuropsychological assessments was 0.12 (range, 13) months, (b) MRI and cardiovascular studies was 3.3 (range, 24) months, and (c) neuropsychological and cardiovascular assessments was 3.4 (range, 24) months. Written informed consent was obtained from participants or, if applicable, their legal representative. Ethical approval was obtained from the National Healthcare Group Domain-Specific Review Board. This study was conducted in accordance with the Declaration of Helsinki.

Vascular Studies

Carotid vascular studies were performed with the ProSound Alpha 10 ultrasound system (Hitachi Aloka Medical Ltd, Tokyo, Japan) at the Cardiovascular Imaging Core Laboratory, National University Health Systems, Singapore. Measures of carotid artery stiffness were obtained using the eTRACKING method, which digitally tracks real-time motion of opposed common carotid artery walls to 0.01-mm resolution at 10 MHz by using radiofrequency signals. The software ensemble averages multiple (typically 15) distension waveforms and calculates several carotid stiffness parameters[21]:

1. The Peterson pressure-strain elastic modulus (Ep), which refers to the resistance to being deformed elastically when stress is applied, expressed as follows: (Ps–Pd)/[(Ds–Dd)/Dd], where Ps = systolic blood pressure, Pd = diastolic blood press, Ds = maximum vessel diameter, and Dd = minimum vessel diameter.
2. The β stiffness index (β-index), which is a relatively blood pressure–independent stiffness index, expressed as log-transformed (Ps/Pd)/[(Ds–Dd)/Dd].
3. One-point PWV-β, which assesses carotid stiffness by deriving the pressure-diameter curve of the artery, and calculating local PWV from the time delay between 2 adjacent distension waveforms. It is expressed as $(\beta P/2\rho)^{1/2}$, whereby β is the stiffness parameter, P is arterial pressure, and ρ is blood density ($1050\,kg^3$).[22]

All carotid stiffness parameters were calculated using central aortic systolic and diastolic pressure obtained with the SphygmoCorPx (AtCor Medical, West Ryde, NSW, Australia). This system uses applanation tonometry to obtain the radial artery waveform and applies a transfer function to convolve radial to aortic pressure.[23]

Neuroimaging

Brain MRI scans were performed on a 3T Siemens Magnetom Trio Tim Scanner, with a 32-channel head receive coil. The standardized neuroimaging protocol included 3-dimensional T1-weighted, T2-weighted, fluid-attenuated inversion recovery, and susceptibility weighted images. Detailed description about the brain MRI protocol was reported in Data S1. Neuroimaging markers of CSVD, including WMHs, lacunes, and cerebral microbleeds, were graded by an expert clinical researcher (S.H.), in accordance with the standardized criteria,[15] as follows:

1. WMHs are hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery sequences, and hypointense lesions on T1-weighted images. The age-related white matter changes scale was used to grade WMHs in 5 different brain locations.[24]
2. Lacunes were identified as round or ovoid lesions that are typically between 3 and 15 mm in size, involving the subcortical regions, with a low signal on T1-weighted images and fluid-attenuated inversion recovery, a high signal on T2-weighted images, and hyperintense rim.[15]
3. Cerebral microbleeds are focal, round hypointense lesions with blooming effect on susceptibility weighted images and were graded using the Brain Observer Microbleed Scale.[25]
4. Significant CSVD was defined as the presence of ≥2 lacunes and/or confluent white matter lesions in 2 regions of the brain (age-related white matter changes score ≥8).

Neuropsychological Assessment

Neuropsychological assessment involved the administration of the National Institute of Neurological Disorders and Stroke and the Canadian Stroke Network harmonization battery that has been validated in our local sample.[26,27] The assessments were administered by research psychologists in the participants' habitual language (eg, English, Chinese, or Malay). The neuropsychological test battery assessed the following 6 cognitive domains:

1. Attention: Digit Span, Visual Memory Spa, and Auditory Detection.
2. Executive function: Frontal Assessment Battery and Maze Task.
3. Language: Boston Naming Test and Verbal Fluency.
4. Visuomotor speed: Symbol Digit Modality Test and Digit Cancellation.
5. Visuospatial function: Weschler Memory Scale—Revised Visual Reproduction Copy Task, Clock Drawing, and Block Design, a subset of Weschler Adult Intelligence Scale—Revised.

6. Memory: Word List Recall, Story Recall, Picture Recall, and Weschler Memory Scale—Revised Visual Reproduction.

All individual test raw scores were transformed into z-scores using the means and SDs of the NCI group. The score for each cognitive domain was computed by averaging the z-scores of individual tests and using the mean and SD of the NCI group. Global cognition z-scores were computed by averaging all the cognitive domain z-scores and using the mean and SD of the NCI group.[25,27,28] Higher z-scores indicate better domain-specific and global cognitive performance.

Diagnosis of Cognitive Impairment

Participants were classified into 4 diagnostic categories based on their clinical features, neuroimaging, psychometrics, and blood investigations at consensus meetings with clinicians and neuropsychologists. Participants were classified as having NCI if they had no objective cognitive impairment on neuropsychological tests or functional loss. Participants were diagnosed with CIND when they had scores <1.5 SDs than the educational-level adjusted cutoff values for each test in at least half the tests in each domain on the neuropsychological test battery, but did not meet the *Diagnostic Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for dementia.[29] Dementia was diagnosed in accordance with *DSM-IV* criteria. The causative diagnoses of dementia followed the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association for Alzheimer disease (AD),[30] and the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche en l'Enseignement en Neurosciences criteria for vascular dementia (VaD).[31] Participants classified as having cognitive impairment included patients with CIND and dementia.

Covariates

A detailed questionnaire was administered to all participants to document social demographic variables: age, sex, and education. Vascular risks factors, such as history of hypertension, diabetes, hyperlipidaemia, and smoking, were noted and verified by medical records. CVDs were defined as having a history of myocardial infarction, atrial fibrillation, coronary angioplasty, coronary bypass surgery, stroke, and heart failure.

Statistical Analysis

Statistical analyses were performed using RStudio 4.0.3 (Boston, MA). The characteristics of the participants were summarized using means and SDs for continuous variables, and numbers and percentages for categorical variables. We transformed all raw values of carotid artery stiffness into standardized z-scores. Dementia (AD and VaD) and its preclinical stages (CIND) were considered as outcomes. Multivariable linear regression with 95% CIs was performed to determine associations between carotid artery stiffness and WMHs. Multivariable logistic regression with odds ratio (OR) and 95% CI was conducted to examine if carotid artery stiffness was associated with presence of lacunes and cerebral microbleeds. The models were adjusted for age, sex, hypertension, diabetes, hyperlipidemia, CVD, and smoking. Similar logistic regression analyses were performed to examine the relationship between carotid artery stiffness and diagnostic groups (ie, CIND and dementia) and for participants with dementia stratified by cause (AD and VaD). The models were adjusted for age, sex, education, hypertension, diabetes, hyperlipidemia, CVD, and smoking. Linear regression models with mean difference and 95% CIs were constructed to investigate the associations between carotid artery stiffness and cognition. All models were first adjusted for age, sex, and education (model 1) and subsequently adjusted for hypertension, diabetes, hyperlipidemia, smoking, and CVD (model 2). Finally, the regression model was additionally adjusted for the presence of lacunes and WMHs (model 3). Additional mediation analyses were conducted to determine the indirect effects of the association between exposure (ie, carotid stiffness) and outcome (ie, cognition) by the mediator (ie, significant CSVD). Carotid stiffness measures that were significantly associated with cognition in model 2 were selected for further mediation analyses. The mediator was defined as presence of significant CSVD, in which participants who were graded ≥8 on the age-related white matter changes scale for WMHs and/or had presence of lacunes on brain MRI scans were considered as having significant CSVD. Mediation models were adjusted for age, sex, education, hypertension, diabetes, hyperlipidemia, CVD, and smoking. For all mediation analyses, we tested the significance of the indirect effects using bootstrapping procedures. Unstandardized indirect effects were computed for each 1000 bootstrapped samples, and 95% CIs were reported. Although 1-tailed $P<0.05$ was considered statistically significant for all analyses, Bonferroni-corrected significance cutoffs were conducted for the multiple testings performed within the 6 cognitive domains for the association between carotid artery stiffness and cognition in model 1, model 2, and model 3, with the resulting 1-tailed $P<0.008$ as statistically significant.

RESULTS

The characteristics of the study sample are presented in Table 1. The mean age of the 272 participants was

Table 1. Characteristics of Study Population

Characteristics	All (N=272)	NCI (n=74)	CIND (n=99)	AD (n=78)	VaD (n=21)
Age, mean (SD), y	75.42 (6.77)	72.93 (7.52)	77.01 (5.87)	75.9 (6.45)	74.67 (7.07)
Sex, n (%)					
Female	157 (57.72)	44 (59)	51 (52)	55 (71)	7 (33)
Education, mean (SD), y	7.32 (5.04)	9.64 (4.82)	8.1 (5.03)	4.63 (4.43)	5.48 (2.52)
Ethnicity, n (%)					
Chinese	237 (87.13)	68 (92)	86 (87)	67 (86)	16 (76)
Malay	18 (6.62)	3 (4)	4 (4)	7 (9)	4 (19)
Indian	14 (5.15)	2 (3)	8 (8)	3 (4)	1 (5)
Others*	3 (1.10)	1 (1)	1 (1)	1 (1)	0 (0)
Vascular risk factors, n (%)					
Hypertension	179 (65.80)	40 (54)	63 (64)	55 (71)	21 (100)
Diabetes	83 (30.51)	12 (16)	28 (28)	32 (41)	11 (52)
Hyperlipidemia	191 (70.22)	53 (72)	67 (68)	53 (68)	18 (86)
Current smoking	12 (4.41)	4 (5)	5 (5)	1 (1)	2 (10)
History of CVD, n (%)					
Myocardial infarction	11 (4.04)	2 (3)	5 (5)	2 (3)	2 (10)
Atrial fibrillation	13 (4.78)	1 (1)	9 (9)	1 (1)	2 (10)
Coronary angioplasty	9 (3.31)	2 (3)	3 (3)	2 (3)	2 (10)
Coronary bypass procedure	7 (2.57)	1 (1)	4 (4)	2 (3)	0 (0)
Heart failure	3 (1.10)	1 (1)	2 (2)	0 (0)	0 (0)
Stroke	49 (18.01)	5 (7)	17 (17)	10 (13)	17 (81)
Blood pressure, mm Hg					
Systolic	142 (19)	139 (19)	140 (18)	147 (21)	147 (18)
Diastolic	73 (11)	73 (10)	71 (10)	74 (11)	78 (14)
Mean arterial pressure, mm Hg	96 (12)	95 (11)	94 (11)	98 (12)	101 (14)
Heart rate, bpm	61 (10)	59 (8)	61 (10)	61 (10)	69 (14)
Pulse pressure, mm Hg	70 (17)	66 (17)	69 (16)	73 (17)	69 (16)

AD indicates Alzheimer disease; bpm, beats per minute; CIND, cognitive impairment no dementia; CVD, cardiovascular disease; NCI, no cognitive impairment; and VaD, vascular dementia.

*Other ethnicities include those who are Eurasians, or have mixed-ethnicities (e.g., Chinese-Malay, Chinese-Indian, Malay-Indian).

75.4±6.8 years, with 58% women and 87% of Chinese ethnicity. Most individuals had cardiovascular risk factors: hyperlipidemia (70%), hypertension (65.8%), and diabetes (30.5%). Of those diagnosed with dementia, 79% had AD and 21% had VaD. Carotid stiffness measures, CSVD, and cognitive performance are further detailed in Table S1.

Associations between carotid artery stiffness and CSVD are shown in Table 2. Increased carotid β-index (β=0.69; *P*=0.002), Ep (β=0.78; *P*<0.001), and PWV-β (β=0.80; *P*<0.001) were associated with WMHs, independent of age, sex, hypertension, diabetes, hyperlipidemia, CVD, and smoking. In addition, Ep (OR, 1.39 [95% CI, 1.04–1.85]) and PWV-β (OR, 1.47 [95% CI,

Table 2. Association Between Carotid Artery Stiffness and CSVD on MRI

Variable	WMHs	Presence of lacunes	Presence of CMBs
	β estimate (95% CI), *P* value	OR (95% CI), *P* value	OR (95% CI), *P* value
β-Index	0.69 (0.26–1.12), *P*=0.002*	1.31 (0.98–1.75), *P*=0.066	1.13 (0.88–1.47), *P*=0.329
Elastic modulus	0.78 (0.35–1.21), *P*<0.001*	1.39 (1.04–1.85), *P*=0.023*	1.10 (0.85–1.42), *P*=0.460
Pulse-wave velocity-β	0.80 (0.37–1.23), *P*<0.001*	1.47 (1.10–1.98), *P*=0.009*	1.07 (0.83–1.38), *P*=0.579

N=272; linear regression model for the association between carotid stiffness and WMH; logistic regression models for the association between carotid stiffness and presence of lacunes and CMBs; all values adjusted for age, sex, hypertension, diabetes, hyperlipidemia, cardiovascular disease, and smoking. CMB indicates cerebral microbleed; CSVD, cerebral small-vessel disease; MRI, magnetic resonance imaging; OR, odds ratio; and WMH, white matter hyperintensity.

*Levels of significance, *P*<0.05.

Table 3. Association Between Carotid Artery Stiffness and Dementia Diagnosis, Expressed as ORs With 95% CIs

Variable	CIND (n=98)	Dementia (n=99)
β-Index	1.17 (0.80–1.80)	1.47 (1.00–2.27)
Elastic modulus	1.10 (0.78–1.60)	1.59 (1.06–2.56)*
Pulse-wave velocity-β	1.15 (0.82–1.66)	1.68 (1.13–2.61)*

Logistic regression models adjusted for age, sex, education, hypertension, diabetes, and hyperlipidemia.

CIND indicates cognitive impairment no dementia; and OR, odds ratio.

*Levels of significance, $P<0.05$.

1.10–1.98]) were independently associated with presence of lacunes. Table 3 shows the association between carotid artery stiffness and diagnostic groups (CIND and dementia), with NCI as the comparison group. Ep (OR, 1.59 [95% CI, 1.06–2.56]) and PWV-β (OR, 1.68 [95% CI, 1.13–2.61]) were associated with dementia diagnosis after adjusting for age, sex, education, hypertension, diabetes, hyperlipidemia, CVD, and smoking. There were no associations between carotid artery stiffness and CIND. In Table 4, when dementia was further stratified by its cause (AD and VaD) and NCI as the comparison group, β-index (OR, 2.04 [95% CI, 1.14–4.13]), Ep (OR, 2.22 [95% CI, 1.25–4.42]), and PWV-β (OR, 2.50 [95% CI, 1.36–5.18]) were associated with VaD. There were no associations between carotid artery stiffness and AD.

The association between carotid artery stiffness and cognition after adjusting for age, sex, and education (model 1) is shown in Table 5. The β-index, Ep, and PWV-β were associated with worse performance on global cognition (β-index: β=−0.31, P=0.018; Ep: β=−0.37, P=0.006; PWV-β: β=−0.42, P=0.002) and visuomotor speed (β-index: β=−0.18, P=0.007; Ep: β=−0.20, P=0.003; PWV-β: β=−0.21, P=0.001). Ep (β=−0.31; P=0.007) and PWV-β (β=−0.34; P=0.003) were additionally associated with visuospatial function, and PWV-β was also associated with executive function (β=−0.33; P=0.004). When the models were further adjusted for vascular risk factors and CVD (model 2; Table 6), all 3 stiffness parameters remained associated with global cognition (β-index: β=−0.31, P=0.028; Ep: β=−0.36, P=0.007; PWV-β: β=−0.42, P=0.001) and visuomotor speed (β-index: β=−0.18, P=0.005; Ep: β=−0.19, P=0.003; PWV-β: β=−0.22, P=0.001). PWV-β was also associated with executive function (β=−0.34; P=0.004), visuospatial function (β=−0.33; P=0.004), and memory (β=−0.22; P=0.006). All stated associations with cognitive domains in models 1 and 2 survived multiple comparison. When CSVD markers were adjusted for in model 3 (Table 7), all associations became insignificant, apart from a borderline significant association of PWV-β with global cognition (β=−0.27; P=0.041). Additional mediation analyses were conducted to determine the indirect effects of the association between carotid artery stiffness and cognition that was mediated by CSVD. These showed that CSVD markers partially mediate the association between carotid artery stiffness and cognition (Figures S1–S5).

Table 4. Association Between Carotid Artery Stiffness and Dementia Diagnosis Stratified by Cause, Expressed as ORs With 95% CIs

Variable	AD (n=78)	VaD (n=21)
β-Index	1.36 (0.88–2.18)	2.04 (1.14–4.13)*
Elastic modulus	1.39 (0.93–2.20)	2.22 (1.25–4.42)*
Pulse-wave velocity-β	1.48 (1.00–2.29)	2.50 (1.36–5.18)*

Logistic regression models adjusted for age, sex, education, hypertension, diabetes, and hyperlipidemia.

AD indicates Alzheimer disease; OR, odds ratio; and VaD, vascular dementia.

*Levels of significance, $P<0.05$.

DISCUSSION

The present study found that functional parameters of carotid artery stiffness, β-index, Ep, and PWV-β, were independently associated with brain MRI markers of CSVD. These measures were additionally associated with a dementia diagnosis, specifically VaD rather than AD, and impairments across a swathe of neurocognitive domains, including visuomotor speed, visuospatial function, and executive function. The associations were independent of vascular risk factors and CVD, and thus not attributable to the downstream effects of CVD. They were largely attenuated after adjusting for CSVD markers, suggesting that cerebral microvascular damage partially mediates the effects of carotid stiffening on cognition.

Stiffening of the aorta and other conduit arteries and their associations with CSVD and cognitive decline have previously been studied, with most reporting a positive relationship.[6,14,32] Given the proximity of the common carotid artery to the cerebral beach head and its eminent accessibility to ultrasonic interrogation, carotid biophysical properties might be expected to inform on the state of the cerebral microvasculature.[10] A few studies have documented a link between carotid artery stiffening and CSVD,[19,33,34] whereas there is ambiguity surrounding the reported associations of carotid stiffness and cognitive function.[18–20,35–40] The 2 by far largest of the considered reports, the Maastricht and Rotterdam Scan Studies,[20,35] showed unexpectedly no independent association of carotid stiffness with cognitive performance, in contrast to other studies, including our own community-based study of an aging cohort.[7] These conflicting results could arise from differences in population profile and techniques

Table 5. Linear Regression Models for the Association Between Carotid Artery Stiffness and Cognition (Model 1)

Variable	Global z-scores	Attention	Executive function	Language	Visuomotor speed	Visuospatial function	Memory
β-Index	−0.31 (−0.57 to −0.05), *P*=0.018*	−0.08 (−0.21 to 0.04), *P*=0.189	−0.22 (−0.45 to 0.003), *P*=0.053	−0.40 (−0.88 to −0.09), *P*=0.114	−0.18 (−0.30 to −0.05), *P*=0.007†	−0.27 (−0.49 to −0.05), *P*=0.017	−0.16 (−0.32 to −0.01), *P*=0.039
Elastic modulus	−0.37 (−0.63 to −0.11), *P*=0.006*	−0.11 (−0.23 to 0.02), *P*=0.102	−0.28 (−0.51 to −0.06), *P*=0.014	−0.45 (−0.95 to 0.04), *P*=0.071	−0.20 (−0.32 to −0.07), *P*=0.003†	−0.31 (−0.53 to −0.09), *P*=0.007†	−0.20 (−0.35 to −0.04), *P*=0.015
Pulse-wave velocity-β	−0.42 (−0.67 to −0.16), *P*=0.002*	−0.13 (−0.26 to −0.003), *P*=0.045	−0.33 (−0.56 to −0.11), *P*=0.004†	−0.52 (−1.01 to −0.03), *P*=0.038	−0.21 (−0.34 to −0.09), *P*=0.001†	−0.34 (−0.56 to −0.12), *P*=0.003†	−0.21 (−0.37 to −0.05), *P*=0.009

Data are given as estimate (95% CI), *P* value. N=272; models adjusted for age, sex, and education.
*Level of significance, *P*<0.05.
†Bonferroni-corrected *P* value (0.05/6=0.008), *P*<0.008.

of cognitive testing and stiffness assessment, non-uniform adjustment for confounders, and challenges related to cohort attrition and verification of the diagnosis of dementia in population-based longitudinal studies.[20,35,41] Nevertheless, the evidence supporting a link between cognition and direct measures of carotid stiffness is not definitive and certainly less robust than for systemic arterial stiffness.[9]

Our study differs from the aforementioned studies in several respects. Participants were mostly older subjects referred for memory loss who therefore represent a clinical cohort at high risk of cognitive impairment. This also afforded the opportunity to examine carotid stiffness parameters in relation to clinically adjudicated subtypes of cognitive impairment, which was not feasible in other studies. Compared with healthier population-based cohorts, these memory clinic patients may also have stiffer aortas with therefore less mismatched aortic and carotid impedance, encouraging transmission of destructive pulsatile energy to the cerebral microcirculation,[42,43] and potentially increasing the burden of CSVD for similar degrees of carotid stiffness. Unlike all previous studies, carotid stiffness indexes were derived using central aortic pressures, in recognition of aorta-to-peripheral pulse pressure amplification.[44,45] Uniquely for carotid stiffness-based studies, we adjusted for brain MRI markers of CSVD to examine their potentially indirect effects on cognitive impairment.

Using the same eTRACKING method used in our community-based study,[7] we reconfirm in a memory cohort the association of functional parameters of carotid artery stiffness with cognitive impairment, as well as WMHs and lacunes. Higher carotid Ep and PWV-β were associated with an increased risk of dementia, whereas all 3 stiffness parameters were associated with VaD rather than AD, expectedly because of its vascular pathology. Prior studies have found associations between carotid artery stiffness and lower cognitive performances in age-sensitive domains, such as executive function, processing speed, working memory, and episodic memory.[7,8,19,37] In the current study, although all carotid stiffness parameters were associated with global cognition, PWV-β appeared to be the most robust stiffness parameter, being associated with a broad swathe of neurocognitive domains even after comprehensive adjustment. Nevertheless, these associations were considerably weak and were almost entirely nullified following adjustment for CSVD. Additional mediation analyses confirmed that the associations between carotid artery stiffness and cognition were partially mediated by CSVD. Our findings provide compelling evidence that CSVD (partially) mediates the deleterious effects of carotid stiffening on cognition. They mirror similar findings by the Age, Gene/Environment Susceptibility-Reykjavik Study in relation to aortic stiffness and memory.[46] This same community-based study also used a Duplex technique to assess common carotid artery flow characteristics, and showed that these measures, although significantly associated with memory, processing speed, and

Table 6. Linear Regression Models for the Association Between Carotid Artery Stiffness and Cognition (Model 2)

Variable	Global z-scores	Attention	Executive function	Language	Visuomotor speed	Visuospatial function	Memory
β-Index	−0.31 (−0.58 to −0.05), *P*=0.028*	−0.09 (−0.21 to 0.04), *P*=0.177	−0.22 (−0.45 to 0.002), *P*=0.053	−0.38 (−0.88 to 0.11), *P*=0.130	−0.18 (−0.31 to −0.05), *P*=0.005†	−0.27 (−0.49 to −0.04), *P*=0.020	−0.17 (−0.33 to −0.02), *P*=0.030
Elastic modulus	−0.36 (−0.62 to −0.10), *P*=0.007*	−0.11 (−0.23 to 0.02), *P*=0.096	−0.28 (−0.50 to −0.05), *P*=0.018	−0.43 (−0.93 to 0.07), *P*=0.090	−0.19 (−0.32 to −0.07), *P*=0.003†	−0.30 (−0.52 to −0.07), *P*=0.010	−0.20 (−0.36 to −0.04), *P*=0.012
Pulse-wave velocity-β	−0.42 (−0.68 to −0.16), *P*=0.001*	−0.14 (−0.26 to −0.01), *P*=0.034	−0.34 (−0.56 to −0.11), *P*=0.004†	−0.52 (−1.01 to −0.02), *P*=0.041	−0.22 (−0.34 to −0.09), *P*=0.001†	−0.33 (−0.56 to −0.11), *P*=0.004†	−0.22 (−0.38 to −0.06), *P*=0.006†

Data are given as estimate (95% CI), *P* value. N=272; models adjusted for age, sex, education, hypertension, diabetes, hyperlipidemia, cardiovascular disease, and smoking.
*Level of significance, *P*<0.05.
†Bonferroni-corrected *P* value (0.05/6 =0.008), *P*<0.008.

Table 7. Linear Regression Models for the Association Between Carotid Artery Stiffness and Cognition (Model 3)

Variable	Global z-scores	Attention	Executive function	Language	Visuomotor speed	Visuospatial function	Memory
β-Index	−0.18 (−0.44 to 0.08), *P*=0.173	−0.04 (−0.17 to 0.08), *P*=0.499	−0.10 (−0.33 to 0.12), *P*=0.365	−0.21 (−0.71 to 0.29), *P*=0.417	−0.12 (−0.25 to 0.001), *P*=0.053	−0.18 (−0.40 to 0.05), *P*=0.124	−0.10 (−0.25 to 0.06), *P*=0.22
Elastic modulus	−0.21 (−0.47 to 0.05), *P*=0.116	−0.06 (−0.19 to 0.07), *P*=0.368	−0.14 (−0.37 to 0.08), *P*=0.220	−0.23 (−0.74 to 0.27), *P*=0.364	−0.13 (−0.26 to −0.004), *P*=0.044	−0.20 (−0.42 to 0.03), *P*=0.091	−0.12 (−0.27 to 0.04), *P*=0.15
Pulse-wave velocity-β	−0.27 (−0.53 to −0.01), *P*=0.041*	−0.09 (−0.22 to 0.04), *P*=0.177	−0.20 (−0.43 to 0.02), *P*=0.078	−0.33 (−0.83 to 0.18), *P*=0.204	−0.15 (−0.28 to −0.03), *P*=0.018	−0.23 (−0.46 to −0.01), *P*=0.045	−0.13 (−0.29 to 0.02), *P*=0.10

Data are given as estimate (95% CI), *P* value. N=272; models adjusted for age, sex, education, hypertension, diabetes, hyperlipidemia, cardiovascular disease, smoking, white matter hyperintensities, and presence of lacunes.

*Level of significance, *P*<0.05.

executive function, were no longer predictive following adjustment for brain WMHs.[43] Future studies could explore the relative merits of carotid biophysical vis-à-vis hemodynamic characteristics in predicting CSVD and cognitive impairment, as well as mechanisms other than microvascular damage that could account for the residual association between carotid artery stiffness and cognition, including cerebral hypoperfusion[46,47] and cardioembolism.[48] Furthermore, our findings support the importance of early screening for cognitive impairment in participants who have elevated carotid artery stiffness, CVD, or other vascular risk factors.[49]

STUDY STRENGTHS AND LIMITATIONS

A strength of our study was the availability of both brain MRI markers of CSVD and cognition to explore mechanistic pathways of carotid artery stiffening. In addition, we used an extensive neuropsychological assessment that is a more sensitive tool to measure cognitive change or impairment compared with cognitive screening tests.

Most studies examining the effects of arterial stiffness on cerebrovascular diseases and cognition have used carotid-femoral PWV, the reference standard measure of systemic arterial stiffness.[50] Although there is no consensus on the ideal carotid artery stiffness parameter, we have focused on PWV-β, which correlates well with carotid-femoral PWV,[22] as well as Ep and β-index, which provide for more physiological accounting of regional stiffness than simple compliance by normalizing for vessel size and blood pressure, respectively.[9,44] We did not assess carotid plaque formation, which may be promoted by increased shear strain in the artery, and cause downstream effects that could influence cognition.[9] Given the cross-sectional study design, we could not determine whether carotid artery stiffness contributes to the onset of cognitive impairment and dementia or vice versa. We are also constrained to consider associations and cannot definitively ascribe cause and effect. Another limitation was that a minority of participants (n=36) had measures of vascular function, brain MRI, and cognitive function, performed 1 to 2 years apart. The time delay between measurements may underestimate the relationships between carotid stiffness, CSVD, and cognition. Furthermore, the effect sizes for the association between carotid stiffness and cognition were small, because of our relatively small sample size. As our sample was recruited from a memory clinic, our findings may not be generalizable to the general population.

CONCLUSIONS

Our study demonstrated that increased carotid artery stiffness was linked to increased WMHs and the presence of lacunes, as well as cognitive imparment and dementia. The association between carotid artery stiffness and cognition was in part explained by the presence of CSVD. Elevated carotid artery stiffness may help identify patients with, or at risk for developing, CSVD, cognitive impairment, and dementia, so that timely treatment plans and preventive strategies can be effectively administered. Future studies could ascertain if carotid artery stiffness has a causative role in cognitive impairment and dementia, or serve as a therapeutic target for prevention of vascular brain damage and improvement of cognitive outcomes.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Data S1
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REFERENCES

1. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol*. 2005;25:932–943. doi: 10.1161/01.ATV.0000160548.78317.29
2. Myung Y, Seo HS, Jung IH, Lee NH, Suh J, Choi JH, Cho YH. The correlation of carotid artery stiffness with heart function in hypertensive patients. *J Cardiovasc Ultrasound*. 2012;20:134–139. doi: 10.4250/jcu.2012.20.3.134
3. Hansen L, Robert TW. Is increased arterial stiffness a cause or consequence of atherosclerosis? *Atherosclerosis*. 2016;249:226–227. doi: 10.1016/j.atherosclerosis.2016.04.014
4. Zhang K, Jiang Y, Wang Y, Suo C, Xu K, Zhu Z, Zhu C, Zhao G, Jin L, Ye W, et al. Associations of arterial stiffness and carotid atherosclerosis with cerebral small vessel disease in a rural community-based population. *J Atheroscler Thromb*. 2020;27:922–933. doi: 10.5551/jat.52530
5. van Sloten TT, Sedaghat S, Laurent S, London GM, Pannier B, Ikram MA, Kavousi M, Mattace-Raso F, Franco OH, Boutouyrie P, et al. Carotid stiffness is associated with incident stroke: a systematic review and individual participant data meta-analysis. *J Am Coll Cardiol*. 2015;66:2116–2125. doi: 10.1016/j.jacc.2015.08.888
6. Singer J, Trollor JN, Baune BT, Sachdev PS, Smith E. Arterial stiffness, the brain and cognition: a systematic review. *Ageing Res Rev*. 2014;15:16–27. doi: 10.1016/j.arr.2014.02.002
7. Lim SL, Gao Q, Nyunt MS, Gong L, Lunaria JB, Lim ML, Ling A, Lam CS, Richards AM, Ling LH, et al. Vascular health indices and cognitive domain function: Singapore longitudinal ageing studies. *J Alzheimers Dis*. 2016;50:27–40. doi: 10.3233/JAD-150516
8. Hoth KF, Moreau KL, Weinberger HD, Holm KE, Meschede K, Crapo JD, Make BJ, Moser DJ, Kozora E, Bowler RP, et al. Carotid artery stiffness is associated with cognitive performance in former smokers with and without chronic obstructive pulmonary disease. *J Am Heart Assoc*. 2020;9:e014862. doi: 10.1161/JAHA.119.014862
9. Baradaran H, Gupta A. Carotid artery stiffness: imaging techniques and impact on cerebrovascular disease. *Front Cardiovasc Med*. 2022;9:852173. doi: 10.3389/fcvm.2022.852173
10. van Sloten TT, Stehouwer CD. Carotid stiffness: A novel cerebrovascular disease risk factor. *Pulse*. 2016;4:24–27. doi: 10.1159/000445354
11. Schellinger IN, Mattern K, Raaz U. The hardest part: arterial stiffness in the context of healthy aging. *Arterioscler Thromb Vasc Biol*. 2019;39:1301–1306. doi: 10.1161/ATVBAHA.118.311578
12. Mitchell GF. Effects of central arterial aging on the structure and function of the peripheral vasculature: Implications for end-organ damage. *J Appl Physiol*. 2008;105:1652–1660. doi: 10.1152/japplphysiol.90549.2008
13. O'Rourke MF, Safar M. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension*. 2005;46:200–204. doi: 10.1161/01.HYP.0000168052.00426.65
14. 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. doi: 10.1016/j.neubiorev.2015.03.011
15. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley R, O'Brien JT, Barkhof F, Benavente OR, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol*. 2013;12:822–838. doi: 10.1016/S1474-4422(13)70124-8
16. Hilal S, Tan CS, van Veluw SJ, Xu X, Vrooman H, Tan BY, Venketasubramanian N, Biessels GJ, Chen C. Cortical cerebral microinfarcts predict cognitive decline in memory clinic patients. *J Cereb Blood Flow Metab*. 2020;40:44–53. doi: 10.1177/0271678X19835565
17. Gyanwali B, Shaik MA, Tan BY, Venketasubramanian N, Chen C, Hilal S. Risk factors for and clinical relevance of incident and progression of cerebral small vessel disease markers in an Asian memory clinic population. *J Alzheimers Dis*. 2019;67:1209–1219. doi: 10.3233/JAD-180911
18. Van Den Heuvel DMJ, Ten Dam VH, De Craen AJM, Admiraal-Behloul F, Olofsen H, Bollen EM, Jolles J, Murray HM, Blauw GJ, Westendorp RGJ, et al. Increase in periventricular white matter hyperintensities parallels decline in mental processing speed in a non-demented elderly population. *J Neurol Neurosurg Psychiatry*. 2006;77:149–153. doi: 10.1136/jnnp.2005.070193
19. DuBose LE, Voss MW, Weng TB, Kent JD, Dubishar KM, Lane-Cordova A, Sigurdsson G, Schmid P, Barlow PB, Pierce GL. Carotid β-stiffness index is associated with slower processing speed but not working memory or white matter integrity in healthy middle-aged/older adults. *J Appl Physiol*. 2017;122:868–876. doi: 10.1152/japplphysiol.00769.2016
20. Poels MM, van Oijen M, Mattace-Raso FU, Hofman A, Koudstaal PJ, Witteman JC, Breteler MM. Arterial stiffness, cognitive decline, and risk of dementia: The Rotterdam study. *Stroke*. 2007;38:888–892. doi: 10.1161/01.STR.0000257998.33768.87
21. Carerj S, Nipote C, Zimbalatti C. *A new tool for the evaluation of stiffness vascular parameters in Clinical Practice: eTRACKING*. Messina, Italy: Cardiology Department, University of Messina; 2008. Available at: http://aloka-europe.de/uploaded/File/A_new_tool_for_the_evaluttion_of_stiffness_vascular_parameters_2008(63)MD_SS.pdf
22. Vriz O, Driussi C, La Carrubba S, Di Bello V, Zito C, Carerj S, Antonini-Canterin F. Comparison of sequentially measured Aloka echo-tracking one-point pulse wave velocity with SphygmoCor carotid-femoral pulse wave velocity. *SAGE Open Med*. 2013;1:2050312113507563. doi: 10.1177/2050312113507563
23. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension*. 2001;38:932–937. doi: 10.1161/hy1001.096106
24. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, Wallin A, Ader H, Leys D, Pantoni L, et al. A new rating Scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32:1318–1322. doi: 10.1161/01.STR.32.6.1318
25. Cordonnier C, Potter GM, Jackson CA, Doubal F, Keir S, Sudlow CLM, Wardlaw JM, Salman RA. Improving interrater agreement about brain microbleeds. *Stroke*. 2009;40:94–99. doi: 10.1161/STROKEAHA.108.526996
26. Xu X, Chan QL, Hilal S, Ikram MK, Venketasubramanian N, Tan BY, Dong Y, Chen CL, Collinson SL. The diagnostic utility of the NINDS-CSN neuropsychological battery in memory clinics. *Dement Geriatr Cogn Disord*. 2016;6:276–282. doi: 10.1159/000445050
27. Yeo D, Gabriel C, Chen C, Lee S, Loenneker T, Wong M. Pilot validation of a customized neuropsychological battery in elderly Singaporeans. *Neurol J South East Asia*. 1997;2:123.
28. Wechsler, D., The Wechsler Memory Scale. 1997. 3rd Edition, The Psychological Corporation, San Antonio.
29. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Washington, DC: American Psychiatric Association Publishing; 1994.
30. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology*. 1984l;34:939–944. doi: 10.1212/WNL.34.7.939
31. Román GC, Tatemichi TK, Erkinjuntti T, Cummings JL, Masdeu JC, Garcia JH, Amaducci L, Orgogozo JM, Brun A, Hofman A, et al. Vascular dementia. *Neurology*. 1993;43:250–260. doi: 10.1212/WNL.43.2.250
32. Scuteri A, Tesauro M, Guglini L, Lauro D, Fini M, Di DN. Aortic stiffness and hypotension episodes are associated with impaired cognitive function in older subjects with subjective complaints of memory loss. *Int J Cardiol*. 2013;169:371–377. doi: 10.1016/j.ijcard.2013.09.009
33. de Havenon A, Wong KH, Elkhetali A, McNally JS, Majersik JJ, Rost NS. Carotid artery stiffness accurately predicts white matter hyperintensity volume 20 years later: A secondary analysis of the atherosclerosis risk

in the community study. *Am J Neuroradiol*. 2019;40:1369–1373. doi: 10.3174/ajnr.A6115
34. Brisset M, Boutouyrie P, Pico F, Zhu Y, Zureik M, Schilling S, Dufouil C, Mazoyer B, Laurent S, Tzourio C, et al. Large-vessel correlates of cerebral small-vessel disease. *Neurology*. 2013;80:662–669. doi: 10.1212/WNL.0b013e318281ccc2
35. Rensma SP, Stehouwer CDA, Van Boxtel MPJ, Houben A, Berendschot T, Jansen JFA, Schalkwijk CG, Verhey FRJ, Kroon AA, Henry RMA, et al. Associations of arterial stiffness with cognitive performance, and the role of microvascular dysfunction: The Maastricht study. *Hypertension*. 2020;75:1607–1614. doi: 10.1161/HYPERTENSIONAHA.119.14307
36. Muela HCS, Costa-Hong VA, Yassuda MS, Moraes NC, Memória CM, Machado MF, Bor-Seng-Shu E, Nogueira RC, Mansur AJ, Massaro AR, et al. Higher arterial stiffness is associated with lower cognitive performance in patients with hypertension. *J Clin Hypertens*. 2018;20:22–30. doi: 10.1111/jch.13129
37. Geijselaers SL, Sep SJ, Schram MT, van Boxtel MP, van Sloten TT, Henry RM, Reesink KD, Kroon AA, Koster A, Schaper NC, et al. Carotid stiffness is associated with impairment of cognitive performance in individuals with and without type 2 diabetes: The Maastricht study. *Atherosclerosis*. 2016;253:186–193. doi: 10.1016/j.atherosclerosis.2016.07.912
38. Nieboer D, Douw L, van Dijk BW, Heymans MW, Stam CJ, Twisk JW. Relation between carotid stiffness, cognitive performance and brain connectivity in a healthy middle-aged population: An observational neurophysiological cohort study with magnetoencephalography. *BMJ Open*. 2016;6:e013441. doi: 10.1136/bmjopen-2016-013441
39. Tarumi T, Gonzales MM, Fallow B, Nualnim N, Pyron M, Tanaka H, Haley AP. Central artery stiffness, neuropsychological function, and cerebral perfusion in sedentary and endurance-trained middle-aged adults. *J Hypertens*. 2013;31:2400–2409. doi: 10.1097/HJH.0b013e328364decc
40. Jurasic MJ, Popovic IM, Morovic S, Trkanjec Z, Seric V, Demarin V. Can beta stiffness index be proposed as risk factor for dementia. *J Neurol Sci*. 2009;283:13–16. doi: 10.1016/j.jns.2009.02.339
41. O'Rourke MF, Staessen JA, Vlachopoulos C, Duprez D, Plante GE. Clinical applications of arterial stiffness; definitions and reference values. *Am J Hypertens*. 2002;15:426–444. doi: 10.1016/S0895-7061(01)02319-6
42. Haidar MA, van Buchem MA, Sigurdsson S, Gotal JD, Gudnason V, Launer LJ, Mitchell GF. Wave reflection at the origin of a first-generation branch artery and target organ protection: The AGES-Reykjavik study. *Hypertension*. 2021;77:1169–1177. doi: 10.1161/HYPERTENSIONAHA.120.16696
43. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ó, Garcia M, Aspelund T, Harris TB, Gudnason V, et al. Arterial stiffness, pressure and flow pulsatility and brain structure and function: The age, gene/environment susceptibility--Reykjavik study. *Brain*. 2011;134:3398–3407.
44. Uejima T, Dunstan FD, Arbustini E, Łoboz-Grudzień K, Hughes AD, Carerj S, Favalli V, Antonini-Canterin F, Vriz O, Vinereanu D, et al. Age-specific reference values for carotid arterial stiffness estimated by ultrasonic wall tracking. *J Hum Hypertens*. 2020;34:214–222. doi: 10.1038/s41371-019-0228-5
45. Avolio AP, Van Bortel LM, Boutouyrie P, Cockcroft JR, McEniery CM, Protogerou AD, Roman MJ, Safar ME, Segers P, Smulyan H. Role of pulse pressure amplification in arterial hypertension: experts' opinion and review of the data. *Hypertension*. 2009;54:375–383. doi: 10.1161/HYPERTENSIONAHA.109.134379
46. Duncombe J, Kitamura A, Hase Y, Ihara M, Kalaria RN, Horsburgh K. Chronic cerebral hypoperfusion: A key mechanism leading to vascular cognitive impairment and dementia. Closing the translational gap between rodent models and human vascular cognitive impairment and dementia. *Clin Sci*. 2017;131:2451–2468. doi: 10.1042/CS20160727
47. Ruitenberg A, den Heijer T, Bakker SL, van Swieten JC, Koudstaal PJ, Hofman A, Breteler MM. Cerebral hypoperfusion and clinical onset of dementia: The Rotterdam study. *Ann Neurol*. 2005;57:789–794. doi: 10.1002/ana.20493
48. de Bruijn RF, Portegies ML, Leening MJ, Bos MJ, Hofman A, van der Lugt A, Niessen WJ, Vernooij MW, Franco OH, Koudstaal PJ, et al. Subclinical cardiac dysfunction increases the risk of stroke and dementia: the Rotterdam study. *Neurology*. 2015;84:833–840. doi: 10.1212/WNL.0000000000001289
49. Scuteri A, Benetos A, Sierra C, Coca A, Chicherio C, Frisoni GB, Gasecki D, Hering D, Lovic D, Manios E, et al. Routine assessment of cognitive function in older patients with hypertension seen by primary care physicians: Why and how-a decision-making support from the working group on 'hypertension and the brain' of the European Society of Hypertension and from the European geriatric medicine society. *J Hypertens*. 2021;39:90–100. doi: 10.1097/HJH.0000000000002621
50. Townsend RR, Wilkinson IB, Schiffrin EL, Avolio AP, Chirinos JA, Cockcroft JR, Heffernan KS, Lakatta EG, McEniery CM, Mitchell GF, et al. Recommendations for improving and standardizing vascular research on arterial stiffness: A scientific statement from the American Heart Association. *Hypertension*. 2015;66:698–722. doi: 10.1161/HYP.0000000000000033
51. Hilal S, Cheung CY, Wong TY, Schmetterer L, Chen C. Retinal parameters, cortical cerebral microinfarcts, and their interaction with cognitive impairment. *Int J Stroke*. 2022;174749302210977. doi: 10.1177/17474930221097737

SUPPLEMENTAL MATERIAL

Data S1.

Supplemental Methods – Brain MRI protocol

Participants underwent a 1.5-hour multi-modal MRI scan. Brain MRI scans were acquired at the Clinical Imaging Research Centre, on 3-Tesla MRI scanners with a state-of-the-art 32-channel head coil. Structural images were obtained with the following protocol and sequences:

- **T1-weighted MRI:** High-resolution T1-weighted Magnetization Prepared Rapid Gradient Recalled Echo (MPRAGE) or similar versions were acquired for the whole brain or specific regions of interest.
- **T2-weighted MRI:** T2-weighted images were also acquired using a double spin echo.
- **Fluid Attenuated Inversion Recovery (FLAIR):** FLAIR data were acquired using FSE- IR sequence.
- **Susceptibility weighted imaging (SWI):** SWI data were acquired during GRE sequence.
- **Quality Assurance (QA):** Quality assurance scans were performed on the day when the patient scan is scheduled. The QA scan is acquired using a gradient echo pulse sequence. The QA images were analyzed in regards to signal to noise ratio (SNR), spatial resolution, slice thickness and location.

The standardized protocol for the scanner acquisition parameters is as follows (51);
3D T1-weighted imaging (1.0x1.0x1.0 mm3 voxels, repetition time, TR=2300 ms, time to echo, TE=1.9 ms, inversion time (TI), 900 ms, flip angle 9°, matrix=256×256×180 mm3). 2D multislice T2-weighted (1.0x1.0x3.0 mm3 voxels, TR=3000 ms, TE=10.1 ms, matrix=247x256). 2D multislice fluid-attenuated inversion recovery (FLAIR) images

(1.0x1.0x3.0 mm3; TR=9000 ms; TE=82 ms; TI 2500 ms, matrix=232 x 256). SWI (echo time = 20 ms; repetition time = 27 ms; flip angle = 15 degrees; field of view= 256 mm; field of view= 75%; image matrix = 192×256; slice thickness = 1.50 mm).

Table S1. Characteristics of study population.

	All (N=272)	NCI (n=74)	CIND (n=99)	AD (n=78)	VaD (n=21)
Vascular stiffness					
β-index	12.14 (5.91)	10.73 (4.42)	12.03 (5.90)	12.77 (6.11)	15.01 (8.43)
Elastic modulus	167.06 (90.55)	144.18 (65.67)	161.67 (86.17)	180.13 (94.7)	221.44 (137.12)
Pulse wave velocity-β	7.39 (1.77)	6.91 (1.41)	7.30 (1.67)	7.64 (1.84)	8.50 (2.46)
CSVD markers					
White matter hyperintensities (WMH)	7.09 (3.77)	5.74 (3.68)	6.57 (3.41)	8.17 (3.66)	10.29 (3.49)
Presence of lacunes, n (%)	69 (25.37)	9 (12.16)	24 (24.24)	19 (24.36)	17 (80.95)
Presence of CMBs, n (%)	115 (42.28)	25 (33.78)	43 (43.43)	38 (48.72)	9 (42.86)
Cognition					
Global z-scores	-2.49 (2.55)	-0.11 (1.02)	-1.92 (1.47)	-4.79 (2.24)	-4.98 (2.09)
Attention	7.11 (2.39)	8.47 (2.07)	7.42 (2.21)	5.98 (2.08)	5.36 (1.84)
Executive function	100.39 (42.47)	61.22 (16.77)	95.37 (35.65)	134.29 (32.49)	140.75 (26.18)
Language	13.44 (2.37)	14.74 (0.60)	14.12 (1.03)	11.70 (3.15)	12.05 (2.97)
Visuomotor speed	20.61 (14.54)	35.42 (10.58)	21.72 (10.51)	8.55 (8.38)	7.57 (9.37)
Visuospatial function	20.33 (10.74)	29.01 (5.12)	22.64 (7.99)	12.01 (10.02)	9.55 (8.31)
Memory	7.54 (5.44)	13.60 (4.010	7.69 (4.19)	2.98 (1.75)	2.83 (1.63)

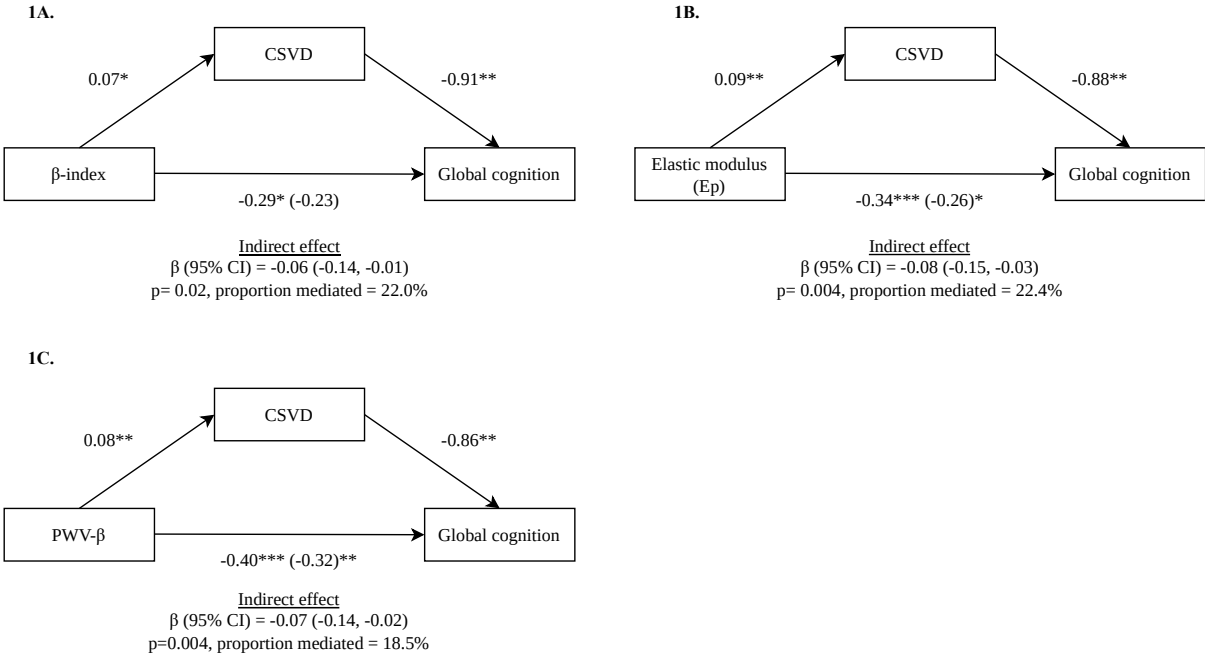

Figure S1. Mediation effect of CSVD on the association between carotid artery stiffness and global cognition. N=272; all models were adjusted for age, sex, education, hypertension, diabetes, hyperlipidaemia, CVD, smoking; *p<0.05, **p<0.01, ***p<0.001.

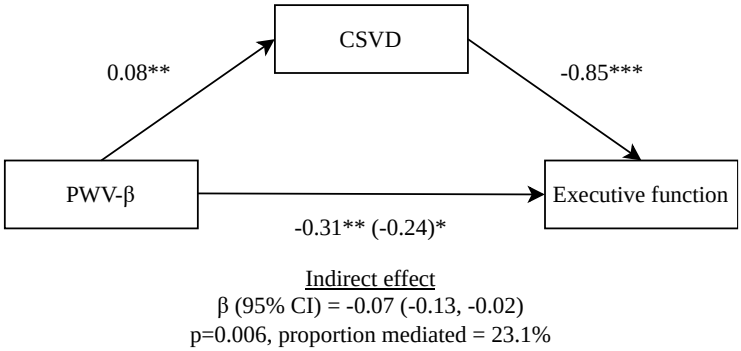

Figure S2. Mediation effect of CSVD on the association between PWV-ß and executive function. N=272; all models were adjusted for age, sex, education, hypertension, diabetes, hyperlipidaemia, CVD, smoking; *p<0.05, **p<0.01, ***p<0.001.

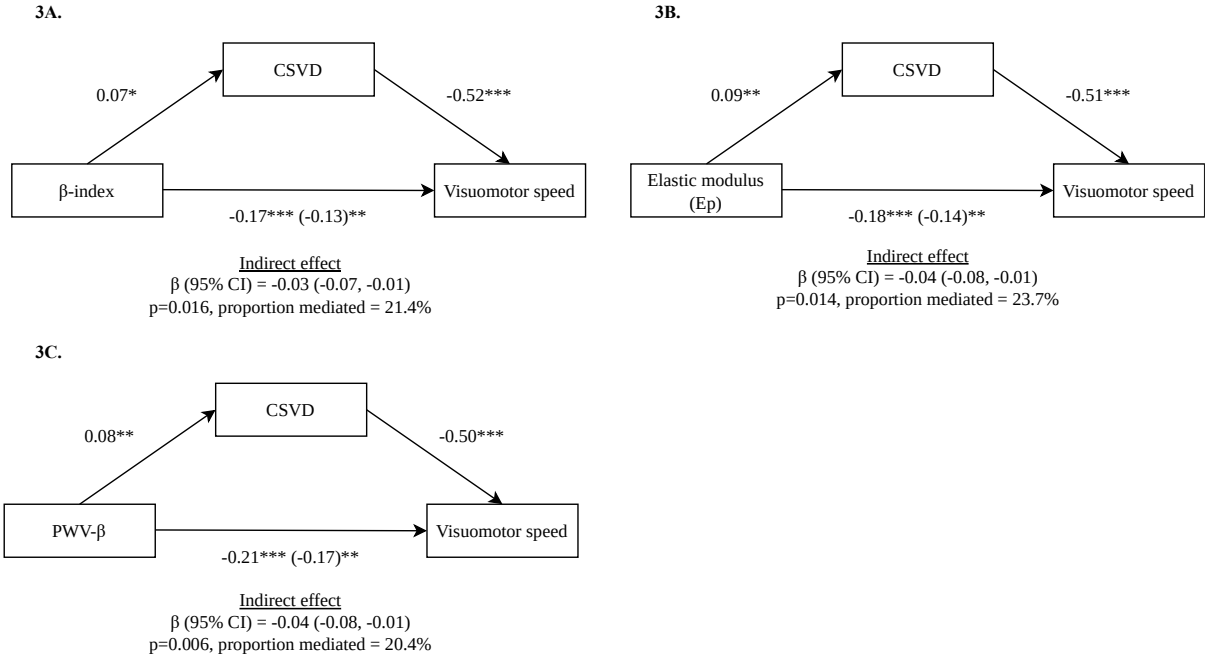

Figure S3. Mediation effect of CSVD on the association between carotid artery stiffness and visuomotor speed. N=272; all models were adjusted for age, sex, education, hypertension, diabetes, hyperlipidaemia, CVD, smoking; *p<0.05, **p<0.01, ***p<0.001.

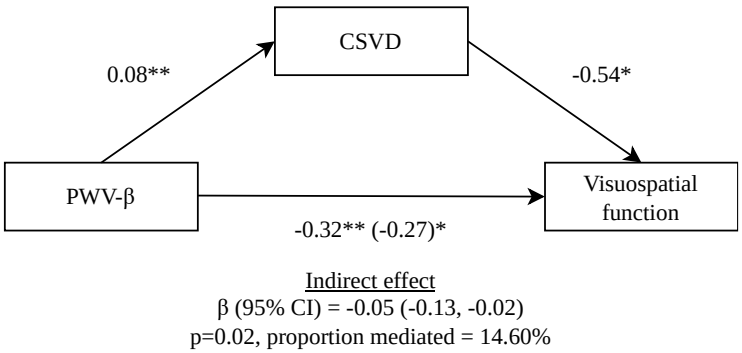

Figure S4. Mediation effect of CSVD on the association between carotid artery stiffness and visuospatial function. N=272; all models were adjusted for age, sex, education, hypertension, diabetes, hyperlipidaemia, CVD, smoking; *p<0.05, **p<0.01, ***p<0.001.

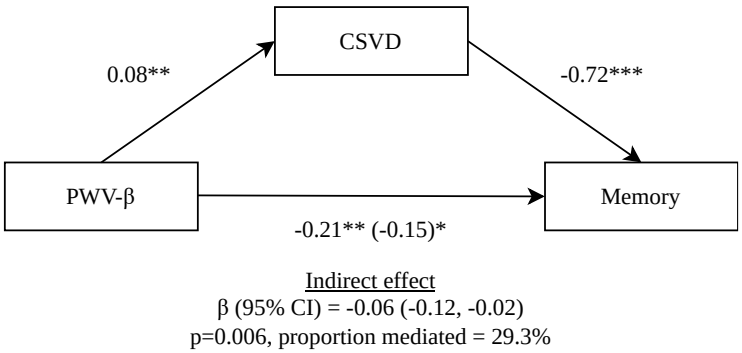

Figure S5. Mediation effect of CSVD on the association between carotid artery stiffness and memory. N=272; all models were adjusted for age, sex, education, hypertension, diabetes, hyperlipidaemia, CVD, smoking; *p<0.05, **p<0.01, ***p<0.001.