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Original Article

Longitudinal associations of carotid artery stiffness with progression of cerebrovascular disease, incident dementia and cognitive decline in older adults

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ABSTRACT

Background: Carotid artery stiffness is associated with cerebrovascular disease (CeVD) and cognitive impairment, but evidence for its longitudinal effects on progression of CeVD and cognitive decline are limited.
Objectives: To evaluate the longitudinal associations of carotid artery stiffness with CeVD progression, incident dementia, and cognitive decline.
Design: Longitudinal analyses from a memory-clinic cohort with a follow-up of 2 years.
Setting: A memory-clinic study.
Participants: 194 participants (mean age=80, 63 % female) with or without cognitive impairments provided consent to take part in the study.
Measurements: Participants underwent carotid ultrasonography, brain MRI, and neuropsychological assessments were at baseline and follow-up. Carotid stiffness measures included ß-index, elastic modulus (Ep), and pulse wave velocity-ß (PWV-ß). CeVD markers included white matter hyperintensities (WMH), lacunes, cerebral microbleeds (CMBs) and cortical infarcts. Cognition was assessed with a neuropsychological battery.
Results: After 2 years, incident CeVD cases included lacunes (15.7 %), CMBs (23.8 %), and cortical infarcts (7.6 %). ß-index (ß=0.78, $p < 0.001$), Ep (ß=0.94, $p < 0.001$), and PWV-ß (ß=0.15, $p = 0.003$) were independently associated with WMH progression. Ep (ß=-0.15, $p = 0.007$) and PWV-ß (ß=-3.68, $p = 0.007$) were independently associated with visuomotor speed decline. No association was found with incident lacunes, CMBs or dementia.
Conclusion: Carotid stiffness progression is associated with WMH progression and visuomotor speed decline.

1. Introduction

Arterial stiffness increases with age and is associated with increased risk for cardiovascular events and mortality[1,2] as well as with cognitive impairment and dementia[3,4]. It has been hypothesized that the mechanisms underlying the associations between arterial stiffness and cognitive impairment involve increased pulsatility and flow load due to arterial stiffening, hence damaging the cerebral vasculature, and contributing to the development of cerebrovascular disease (CeVD)[2,5–7], which are established markers of cognitive impairment and dementia[8,9]. Carotid artery stiffness appears to have a critical role in the pathogenesis of stroke, independent of cardiovascular risk factors (CVRF) and aortic stiffness measured by carotid-femoral pulse wave velocity (cf-PWV)[10]. Previous study had demonstrated the greater effects of carotid artery stiffness on CeVD and cognitive outcomes in memory-clinic patients compared to aortic stiffness, thus suggesting that

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stiffness in the carotid arteries could be more detrimental to cerebral target organ damage due to its closer proximity to the brain[11]. Furthermore, carotid artery stiffness is independently associated with CeVD, vascular dementia, as well as deficits in cognitive function in older adults[12–15].

While most studies on the longitudinal associations of arterial stiffness with CeVD progression and cognitive decline have primarily focused on cf-PWV[3,4,16], research investigating the effects of carotid artery stiffness on these outcomes remains comparatively limited. Findings from longitudinal studies demonstrated that carotid artery stiffening, assessed by carotid strain, distensibility and stiffness index, was associated with progression of white matter hyperintensities (WMH) in the Atherosclerosis Risk in Communities (ARIC) cohort[17], and incident cerebral microbleeds (CMBs) in the AGES-Reykjavik cohort[18]. However, studies examining the associations between changes in carotid artery stiffness over time and progression of other CeVD markers of cognitive impairment such as lacunes are lacking.

With regards to cognitive decline and incident dementia, there is limited evidence to substantiate a significant effect of carotid artery stiffness. This is largely due to the mixed findings related to carotid intima-media thickness (CIMT) and carotid distensibility, which have been the primary focus of most studies, as well as the lack of research investigating other markers of carotid artery stiffness. CIMT has been associated with declines in the cognitive domain of processing speed[19], but not with other cognitive domains[20]. Furthermore, associations between CIMT and incident dementia have been inconsistent[21,22]. For instance, carotid distensibility was not associated with cognitive decline or incident dementia in community-based Rotterdam Study[23]. However, in a different cohort of women with or at risk of HIV, carotid distensibility was associated with cognitive decline[24]. Therefore, the associations between carotid artery stiffness, cognitive decline and incident dementia remain inconclusive.

As previously mentioned, most studies examining the effects of carotid artery stiffness on CeVD progression and cognitive decline have primarily focused on CIMT and carotid distensibility. While these markers provide valuable insights into arterial structure and elasticity respectively, they do not fully capture the mechanical properties of the carotid artery that are crucial for understanding vascular contributions to cognitive impairment and dementia. To address this gap, our study aims to investigate the associations of carotid artery stiffness, measured by carotid ß-stiffness index (ß-index), elastic modulus (Ep), and local pulse wave velocity (PWV-ß) with CeVD progression, incident dementia and cognitive decline over a 2-year follow-up in a cohort of older adults from a memory clinic. We hypothesize that all measures of carotid artery stiffness (ß-index, Ep, and PWV-ß) are associated with CeVD progression, incident dementia and cognitive decline.

2. Methods

2.1. Study population

Participants were recruited from an on-going memory clinic-based study at the National University Hospital, Singapore. Participants who were identified in the following diagnostic categories at baseline were considered eligible for inclusion in the study: no cognitive impairment (NCI), cognitive impairment no dementia (CIND), and dementia. Participants with major psychiatric illness or substance abuse disorders, cognitive impairment caused by a history of traumatic brain injury, multiple sclerosis, tumour, epilepsy or systemic disease, and significant visual and auditory impairments were excluded from the study. All participants underwent comprehensive evaluation, including physical, medical, and neuropsychological assessments, along with 3T brain MRI. Between August 2015 and February 2020, a total of 272 participants were enrolled in a cardiovascular sub-study, where they additionally underwent a 12-lead ECG and vascular imaging. Two years after their baseline evaluation, participants returned for a follow-up, which included repeat assessments of all baseline measures. After excluding participants who did not meet inclusion criteria for the follow-up assessment (n = 7), declined to participate (n = 43), had no follow-up (n = 13) or were deceased (n = 15), 207 participants attended the follow-up assessment. We further excluded participants with incomplete data (n = 22), resulting in a final sample of 172 participants for the longitudinal analyses (Fig. 1). Written informed consent was obtained from participants or, if applicable, their legal representatives. Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board. The study was conducted in accordance with the Declaration of Helsinki.

2.2. Vascular assessment

Vascular assessments at the Cardiovascular Imaging Core Laboratory, National University Health Systems, Singapore. Carotid vascular investigations were performed using the ProSound Alpha 10 ultrasound system (Hitachi Aloka Medical Ltd, Tokyo, Japan). Carotid artery stiffness measurements were primarily obtained from the right carotid artery using the eTracking method, which digitally tracks real-time motion of the opposed common carotid artery walls with a resolution of 0.01 mm at 10 MHz using radiofrequency signals. The software ensemble averages multiple (typically 15) distension waveforms and calculates the following carotid artery stiffness parameters[25]:

1. The Peterson pressure-strain elastic modulus (Ep), which refers to the resistance to being deformed elastically when stress is applied, expressed as follows: (SBP−DBP)/[(Ds−Dd)/Dd], where 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 (SBP/DBP)/[(Ds−Dd)/Dd].
3. One-point pulse wave velocity (PWV-β), which assesses carotid stiffness by deriving the pressure-diameter curve of the artery, and calculating local PWV from the time delay between two adjacent distension waveforms. It is expressed as $(\beta \times SBP/2\rho)^{1/2}$, whereby β is the stiffness parameter, and ρ is blood density ($1050 kg^3$) [26].

In summary, the ß-index offers a stable measure of intrinsic arterial stiffness, independent of blood pressure variations, while local PWV and elastic modulus provide direct evaluations of arterial wall elasticity and mechanical properties[27]. All carotid artery stiffness parameters were calculated using central aortic SBP and DBP obtained with the SphygmoCorPx system.

2.3. 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 3dimensional T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and susceptibility weighted images (SWI). All MRI scans were visually graded for neuroimaging markers of CeVD, including WMH, lacunes, cerebral microbleeds, cortical infarcts, and intracranial stenosis were graded by 2 independent raters, and in accordance with the standardized criteria as follows[8,9]:

1. White matter hyperintensities (WMH): WMH are hyperintense lesions on T2-weighted and FLAIR and appear hypointense on T1-weighted images. The severity of WMH was graded using the age-related white matter changes (ARWMC) scale, in which WMH in 5 different brain locations (frontal, parietal-occipital, temporal, basal ganglia, infratentorial) was assessed[28]. Lesions in each brain region were graded on a scale: no lesions (0), focal lesions (1), confluent lesions (2), and diffuse WMH involvement (3). The total ARWMC score was obtained by summing the scores across all five brain regions, resulting in a total score ranging from 0 to 30.

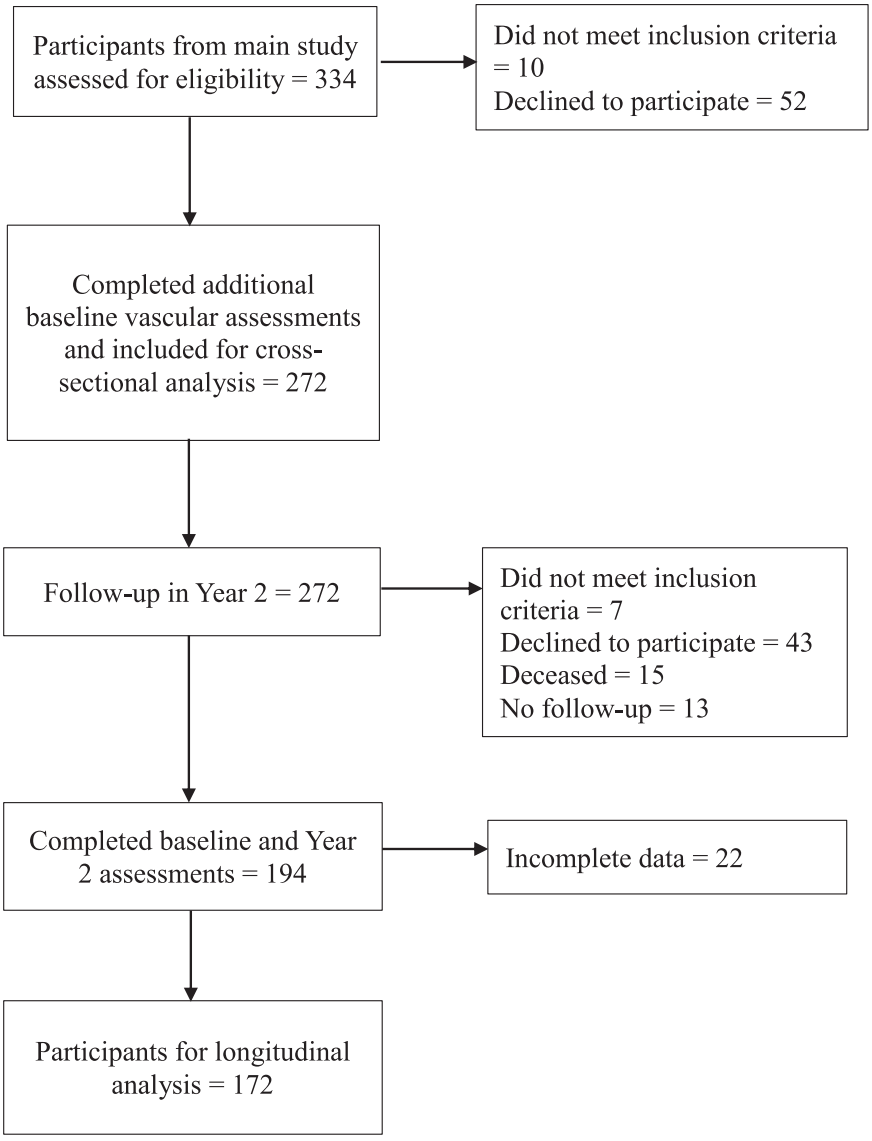

Fig. 1. Study flow of participants in the memory-clinic cohort in Singapore.

2. Lacunes: Lacunes were identified as round or ovoid lesions that are typically between 3 and 5 mm in size. They are located in the subcortical regions of the brain, with a low signal on T1-weighted images, a low signal with a hyperintense rim on FLAIR, and a high signal on T2-weighted images.
3. Cerebral microbleeds (CMBs): CMBs are focal, round, hypointense lesions with a blooming effect on SWI. CMBs were graded using the Brain Observer Microbleed Scale[29].
4. Cortical infarcts: Cortical infarcts was defined as focal lesions with a low signal on T1-weighted images, and a high signal on T2-weighted images.

2.4. Neuropsychological assessments

Participants underwent comprehensive neuropsychological assessment in their habitual language (e.g., English, Chinese, Malay). The neuropsychological assessments included the Mini-Mental State Examination (MMSE)[30], Montreal Cognitive Assessment (MoCA)[31] and the National Institute of Neurological Disorders and Stroke - Canadian Stroke Network harmonization battery (NINDS-CSN) that has been validated in Singapore[32,33]. The assessments were administered by research psychologists in the participants' habitual language (e.g., English, Chinese, or Malay). The neuropsychological test battery assessed the following6 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.

2.5. 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 no cognitive impairment (NCI) if

they had no objective cognitive impairment on neuropsychological tests or functional loss. These NCI participants may have subjective memory complaints but had no objective cognitive impairment on formal neuropsychological testing. Participants were diagnosed with cognitive impairment no dementia (CIND) when they had scores <1.5 SDs than the educational-level adjusted cut-off 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[34]. Dementia was diagnosed in accordance with DSM-¬IV criteria. The causative diagnoses of dementia were made in accordance with the National Institute of Neurological and Communicative Disorders and Stroke–¬Alzheimer's Disease and Related Disorders Association for Alzheimer disease (AD)[35], and the National Institute of Neurological Disorders and Stroke–¬Association Internationale pour la Recherche en l'Enseignement en Neurosciences criteria for vascular dementia (VaD)[36].

2.6. Covariates

Participants' sociodemographic information, including age, sex, and education, was treated as covariates. Vascular risk factors such as history of hypertension, diabetes, hyperlipidemia, and smoking status were also noted and verified by medical records. Participants were also enquired if they had any history of cardiovascular disease (CVD), such as having a history of myocardial infarction, atrial fibrillation, coronary angioplasty, coronary bypass surgery, stroke, and heart failure.

2.7. Statistical analysis

Statistical analyses were performed with 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. Serial change in carotid artery stiffness was treated as exposure outcomes. The difference between all raw values of carotid artery stiffness, including ß-index, Ep, and PWV-ß, at baseline and at follow-up were calculated and transformed into standardized z-scores. Positive values indicate an increase or worsening (progression) in carotid artery stiffness over time. The progression of white matter hyperintensities (WMH), defined as an increase in ARWMC from baseline to follow-up, as well as incident lacunes, cerebral microbleeds (CMBs), and cortical infarcts, were also treated as outcomes. Additionally, the transition from no cognitive impairment (NCI) and preclinical stages of dementia (CIND) to dementia, including its subtypes Alzheimer's disease (AD) and vascular dementia (VaD), was treated as outcomes. Cognitive decline was assessed by the deterioration of cognitive performance over time. Box plots or scree plots were constructed to determine the association between carotid artery stiffness parameters and CeVD (supplementary material, figures S1-S7).

The associations of carotid artery stiffness with progression of WMH and cognitive decline were analyzed using generalized estimating equation (GEE) with independent correlation structure, accounting for correlations between repeated measurements over time. This approach allowed us to assess the longitudinal associations of carotid artery stiffness with WMH and cognitive decline, while modeling changes in both carotid artery stiffness and outcomes across follow-up visits. Model 1 showed the unadjusted model. In Model 2, covariates including age, sex, hypertension, diabetes, hyperlipidemia, CVD, and smoking were adjusted. Where cognitive decline was the outcome, education was additionally adjusted for in Model 2.

Firth regression analyses with 95 % confidence intervals (CI) were conducted for the associations between changes in carotid artery stiffness over time (i.e., change in ß-index, Ep, PWV-ß) and incident CeVD (i.e., incident lacune, CMB, and cortical infarcts). Model 1reported the unadjusted model. In Model 2, adjustment for covariates included age, sex, hypertension, diabetes, hyperlipidemia, CVD, smoking, and baseline measure of the carotid artery stiffness parameter corresponding to each exposure. Specifically, when change in ß-index, Ep, or PWV-ß was the exposure, only the baseline value of that respective parameter was adjusted for in the model.

Complete case analysis was employed for all statistical analyses. Statistical significance was considered at $p < 0.05$. Bonferroni-corrected significance cutoffs were used for the multiple testing performed within 6 cognitive domains for the associations between carotid artery stiffness and cognitive decline, thus resulting in $p < 0.008$.

3. Results

Table 1 shows the study population characteristics. The mean age of the participants at the baseline assessment was 80 (SD 9) years, 62.8 % were female, and 91 % of Chinese ethnicity. A high proportion of the participants had cardiovascular risk factors at baseline: 71.5 % hyper-

Table 1
Characteristics of study population.

	Baseline assessment (N = 172)	Follow-up assessment (N = 172)
Age, mean (SD)	78.8 (9.0)	80.8 (9.0)
Sex, n (%)		
Male	64 (37.2 %)	64 (37.2 %)
Female	108 (62.8 %)	108 (62.8 %)
Years of Education, mean (SD)	7.1 (5.1)	7.04 (5.1)
Ethnicity		
Chinese	156 (90.7 %)	157 (91.3 %)
Malay	9 (5.2 %)	9 (5.2 %)
Indian	6 (3.5 %)	5 (2.9 %)
Other	1 (0.6 %)	1 (0.6 %)
Vascular risk factors, n (%)		
Hypertension	112 (65.1 %)	113 (65.7 %)
Diabetes	44 (25.6 %)	45 (26.2 %)
Hyperlipidemia	123 (71.5 %)	123 (71.5 %)
Current smoking	9 (5.2 %)	9 (5.2 %)
History of CVD, n (%)		
Myocardial infarction	7 (4.1 %)	7 (4.1 %)
Atrial fibrillation	7 (4.1 %)	7 (4.1 %)
Coronary angioplasty	6 (3.5 %)	6 (3.5 %)
Coronary bypass	3 (1.7 %)	3 (1.7 %)
Stroke	23 (13.4 %)	23 (13.4 %)
Dementia, n(%)	49 (28.5 %)	64 (37.2 %)
Blood pressure, mmHg, mean (SD)		
Systolic blood pressure	142 (20.0)	144 (20.6)
Diastolic blood pressure	73.5 (10.8)	73.5 (8.6)
Heart rate, bpm	62.1 (10.7)	66.8 (40.7)
Vascular stiffness, mean (SD)		
ß-index	13.3 (6.4)	13.4 (5.1)
Elastic modulus (Ep)	183 (96.7)	187 (84.8)
PWV-ß	7.63 (1.7)	12.0 (55.6)
CeVD markers		
ARWMC, mean (SD)	6.62 (3.7)	6.68 (3.8)
Presence of lacune, n (%)	42 (24.4 %)	51 (29.7 %)
Presence of CMB, n (%)	73 (42.4 %)	77 (44.8 %)
Presence of cortical infarct, n (%)	14 (8.1 %)	23 (13.4 %)
Presence of stenosis, n (%)	10 (5.8 %)	10 (5.8 %)
Cognition		
MMSE, mean (SD)	22.5 (5.9)	21.6 (7.2)
MoCA, mean (SD)	19.0 (7.0)	18.3 (8.3)
Global z-score (median, IQR)	−1.5 (−3.8, −0.2)	−1.8 (−4.6, −0.2)
Attention z-score (median, IQR)	−0.6 (−1.4, 0.2)	−0.9 (−1.6, 0.2)
Executive function z-score (median, IQR)	−1.4 (−4.2, −0.2)	−1.7 (−4.8, −0.0)
Language z-score (median, IQR)	−0.5 (−3.2, 0.4)	−1.2 (−4.3, 0.4)
Visuomotor speed z-score (median, IQR)	−1.2 (−2.5, −0.4)	−1.5 (−2.7, −0.4)
Visuospatial function z-score (median, IQR)	−1.2 (−3.6, 0.2)	−1.3 (−3.9, 0.1)
Memory z-score (median, IQR)	−1.5 (−2.7, −0.5)	−2.1 (−3.3, −0.6)

lipidemia, 65.1 % hypertension, and 25.6 % diabetes. At follow-up, incident CeVD events included: 27 lacunes, 41 CMB, and 13 cortical infarcts.

The associations between changes in carotid artery stiffness over time and progression of CeVD are presented in Table 2. Increased ß-index (ß =0.783, $p < 0.001$), Ep (ß =0.942, $p < 0.001$), and PWV-ß (ß=0.153, $p < 0.001$) over time were associated with WMH progression at follow-up, independent of age, sex, vascular risk factors and CVD. Increased ß-index (OR=0.284, 95 %CI 0.069 – 0.818) and Ep (OR=0.303 (0.079 – 0.821) over time were associated with reduced risk of incident cortical infarcts, independent of the baseline measure of carotid artery stiffness (i.e., ß-index, Ep), age, sex, vascular risk factors and CVD. No associations were found for any measure of carotid artery stiffness with incident lacune and CMB. Similarly, changes in ß-index (OR=0.683, 95 % CI 0.282 – 1.440), Ep (OR=0.677, 95 % CI 0.291 – 1.362), and PWV-ß (OR=1.051, 95 % CI 0.706 – 1.354) were not associated with incident dementia after adjusting for age, sex, education, vascular risk factors and CVD (all $p > 0.05$).

Table 3 presents the associations between changes in carotid artery stiffness parameters over time with cognitive decline. Our findings indicated that ß-index, Ep, and PWV-ß were negatively associated with global cognition z-scores and all cognitive domains, except for the language domain, in unadjusted Model 1. After adjusting for covariates in Model 2, most of the associations between carotid artery stiffness and cognitive decline were attenuated and became non-significant. Nonetheless, after applying Bonferroni-corrected significance thresholds, the associations of Ep (ß=−0.150, $p = 0.007$) and PWV-ß (ß=−3.684, $p = 0.007$) remained negatively associated with decline in the visuomotor speed domain.

4. Discussion

In this study, we examined the longitudinal associations of carotid artery stiffness with progression of CeVD, incident dementia and cognitive decline over a 2-year period in a hospital-based cohort. Our results indicated that changes in carotid artery stiffness over time, as measured by ß-index, Ep, and PWV-ß, was independently associated with progression of WMH. Interestingly, increased ß-index and Ep over time were associated with reduced risk of incident cortical infarcts. Furthermore, increased Ep and PWV-ß over time were significantly associated with a decline in visuomotor speed at follow-up. These associations persisted even after adjusting for age, sex, vascular risk factors, and CVD.

Evidence from the community-based ARIC study had found support for the association between carotid artery stiffness (measured by Ep and ß-index) and the progression of WMH volume over a 20-year follow-up period[17]. Findings from the current study are consistent with this, and despite the shorter follow-up duration of 2 years, progression of WMH were still detected in our hospital-based cohort. Increased stiffness in the carotid arteries can lead to elevated pulsatile stress on the cerebral vasculature, impair cerebral autoregulation causing chronic ischemia, promote endothelial dysfunction that compromises the blood-brain barrier, and atherosclerotic plaque formation, all of which can contribute to WMH development and progression[6]. However, the changes in carotid artery stiffness, particularly ß-index and Ep, was unexpectedly found to be associated with a reduced risk of incident cortical infarcts. While increased carotid stiffening usually indicates a higher risk for vascular events, vascular adaptation and compensatory mechanisms may mitigate this risk over time. For instance, enhanced collateral circulation may develop in response to reduced vascular compliance in the carotid arteries, thus ensuring adequate cerebral perfusion and potentially lowering stroke risk[37]. Additionally, autoregulation responses may adjust vascular resistance in downstream vessels to maintain sufficient cerebral blood flow[38]. Given the two-year follow-up period in our study, this timeframe may not be sufficient to fully capture the long-term detrimental effects of carotid artery stiffening on risk of incident cortical infarcts.

This study also did not find associations between carotid artery stiffness and other CeVD markers such as lacunes, and CMBs. Previous findings from the SMART-MR study, similarly reported no associations between carotid distensibility and incident brain infarcts in a cohort of patients with arterial disease after a 4-year follow-up[39]. In contrast, the larger epidemiological MESA study found that carotid distensibility and stenosis were associated with incident ischemic stroke[40]. Additionally, the AGES-Reykjavik Study found that carotid artery stiffening was associated with an increased risk of incident deep CMBs after a 5-year follow-up. Several factors might explain the lack of associations found between carotid artery stiffness and other CeVD markers in the current study. Participants from the current study were recruited from a memory clinic, where they may be receiving treatment to manage their vascular risk factors, thereby mitigating the severity of carotid artery stiffness and preventing further brain damage. Additionally, the small number of incident cases during our 2-year follow-up might have resulted in insufficient statistical power to detect associations between carotid artery stiffness and these outcomes.

We had previously found that carotid artery stiffening was independently associated with vascular dementia in the hospital-based cohort[15]. However, after a 2-year follow-up of the same cohort, no associations were found between carotid artery stiffness and incident dementia in the current study, likely due to the small number of dementia cases observed during follow-up period, with 12 participants developing

Table 2
Associations between changes in carotid artery stiffness over time and CeVD progression.

Carotid artery stiffness	WMH Estimate, *p*-value	Incident lacune ($n = 27$) OR (95 % CI), *p*-value	Incident CMB ($n = 41$)	Incident cortical infarct ($n = 13$)
ß-index				
Model 1	**0.905, $p < 0.001$**	0.766 (0.532, 1.117), $p = 0.158$	0.949 (0.683, 1.356), $p = 0.765$	**0.627 (0.403, 0.980), $p = 0.041$***
Model 2	**0.783, $p < 0.001$**	0.925 (0.497, 1.617), $p = 0.789$	1.383 (0.838, 2.307), $p = 0.202$	**0.284 (0.069, 0.818), $p = 0.016$***
Elastic modulus (Ep)				
Model 1	**1.083, $p < 0.001$**	0.741 (0.510, 1.083), $p = 0.118$	0.985 (0.704, 1.412), $p = 0.929$	**0.607 (0.384, 0.960), $p = 0.034$***
Model 2	**0.942, $p < 0.001$**	1.005 (0.580, 1.674), $p = 0.986$	1.426 (0.900, 2.294), $p = 0.130$	**0.303 (0.079, 0.821), $p = 0.015$***
PWV-ß				
Model 1	**0.228, $p < 0.001$**	1.039 (0.698, 1.303), $p = 0.771$	1.191 (0.951, 1.760), $p = 0.125$	1.105 (0.744, 1.388), $p = 0.488$
Model 2	**0.153, $p = 0.003$**	1.016 (0.690, 1.285), $p = 0.901$	1.199 (0.950, 1.784), $p = 0.125$	1.059 (0.711, 1.353), $p = 0.686$

Note: GEE analysis was conducted for the associations between carotid artery stiffness and changes in WMH over time. Model 1 was unadjusted. Model 2 adjusted for age, sex, hypertension, diabetes, hyperlipidemia, CVD, smoking.
Firth regression analyses were conducted for the associations between carotid artery stiffness and incident lacunes, CMB and cortical infarcts. Firth regression model 1 was unadjusted. Firth regression model 2 adjusted for age, sex, hypertension, diabetes, hyperlipidemia, CVD, smoking, and baseline carotid artery stiffness.
* Level of significance, $p < 0.05$.

Table 3
Associations between carotid artery stiffness and cognitive decline.

	MMSE	MoCA	Global z-scores	Attention	Executive function	Language	Visuomotor speed	Visuospatial function	Memory
	Estimate, p-value								
ß-index									
Model 1	**−0.199, $p = 0.002$***	**−0.204, $p = 0.005$***	**−0.547, $p < 0.001$***	**−0.188, $p = 0.005$**^	**−0.536, $p < 0.001$**^	−0.462, $p = 0.070$	**−0.388, $p < 0.001$**^	**−0.412, $p = 0.002$**^	**−0.332, $p < 0.001$**^
Model 2	−0.034, $p = 0.602$	−0.026, $p = 0.707$	−0.070, $p = 0.635$	−0.026, $p = 0.713$	−0.047, $p = 0.725$	0.023, $p = 0.932$	−0.132, $p = 0.015$	−0.024, $p = 0.845$	−0.080, $p = 0.284$
Elastic modulus (Ep)									
Model 1	**−0.239, $p < 0.001$***	**−0.245, $p = 0.001$***	**−0.674, $p < 0.001$***	**−0.235, $p = 0.001$**^	**−0.643, $p < 0.001$**^	−0.637, $p = 0.015$	**−0.443, $p < 0.001$**^	**−0.502, $p < 0.001$**^	**−0.405, $p < 0.001$**^
Model 2	−0.052, $p = 0.449$	−0.041, $p = 0.573$	−0.135, $p = 0.372$	−0.053, $p = 0.474$	−0.094, $p = 0.501$	−0.093, $p = 0.735$	**−0.150, $p = 0.007$**^	−0.064, $p = 0.623$	0.623, $p = 0.148$
PWV-ß									
Model 1	**−5.721, $p < 0.001$***	**−6.007, $p < 0.001$***	**−15.601, $p < 0.001$***	**−5.822, $p < 0.001$**^	**−15.113, $p < 0.001$**^	−13.854, $p = 0.029$	**−10.251, $p < 0.001$**^	**−11.653, $p < 0.001$**^	**−9.715, $p < 0.001$**^
Model 2	−1.557, $p = 0.302$	−1.461, $p = 0.338$	−3.693, $p = 0.294$	−1.779, $p = 0.326$	−2.862, $p = 0.361$	−2.012, $p = 0.760$	**−3.684, $p = 0.007$**^	−2.112, $p = 0.477$	−3.250, $p = 0.072$

Model 1 was unadjusted. Model 2 adjusted for age, sex, hypertension, diabetes, hyperlipidemia, CVD, smoking.
* Level of significance, $p < 0.05$.
^ Bonferroni-corrected p-value ($0.05/6 = 0.008$), $p < 0.008$.

Alzheimer's disease and only 3 developing vascular dementia. Despite the lack of associations with incident dementia, carotid artery stiffening was associated with a decline in visuomotor speed, a cognitive domain that is particularly susceptible to vascular pathology such as cerebral small vessel disease[41,42]. Future longitudinal studies with longer follow-up duration are needed to ascertain the clinical utility of carotid artery stiffness in predicting cognitive impairment and incident dementia. Furthermore, structural parameters of carotid artery function may also play a role in the development and progression of CeVD. Future research should integrate structural markers such as CIMT and carotid stenosis alongside functional measures of carotid stiffness to better delineate their respective contributions to CeVD pathophysiology.

A strength of the current study includes the utilization of comprehensive neuropsychological assessments to examine decline not just in global cognition, but also in specific cognitive domains. A potential limitation of this study is the possibility of a ceiling effect due to the advanced age and high burden of cardiovascular risk factors in the cohort. Many participants may have already accumulated substantial cerebrovascular damage, which could have limited the ability to detect additional effects of carotid artery stiffness on CeVD progression and cognitive decline. However, our analyses accounted for age as a covariate, ensuring that the observed associations between carotid artery stiffness, CeVD progression and cognitive decline were independent of age-related effects. Despite this, the influence of long-term exposure to vascular pathology in this older cohort should be considered when interpreting the findings. The relatively short 2-year follow-up period also poses a challenge in detecting significant changes in the brain, cognitive decline, or progression of cognitive impairment and dementia. The small sample size also limited the number of incident cases observed, possibly resulting in underpowered statistical analyses. Additionally, our findings may not be generalizable to the wider population, as we recruited older participants from a memory clinic.

In conclusion, our study demonstrated the independent association between increased carotid artery stiffness and the progression of WMH, as well as its impact on visuomotor speed decline over a 2-year follow-up period in a memory-clinic patient cohort. We did not find support for the association between carotid artery stiffness and incident dementia, possibly due to the small number of incident cases and relatively short follow-up duration. Nevertheless, the ability of carotid artery stiffness to detect subclinical changes, such as WMH progression and visuomotor speed decline, underscores its potential value in identifying early cognitive decline before the onset of clinical dementia. Future research should address these limitations by incorporating longer follow-up periods, larger and more diverse sample sizes, and examining healthy cohorts to fully elucidate the role of carotid artery stiffness in cerebrovascular and cognitive health.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Caroline Robert: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Lieng-Hsi Ling:** Writing – review & editing, Resources, Methodology. **Eugene S.J. Tan:** Writing – review & editing, Investigation. **Narayanaswamy Venketasubramanian:** Writing – review & editing, Investigation. **Shir Lynn Lim:** Writing – review & editing, Methodology, Investigation. **Lingli Gong:** Writing – review & editing, Methodology, Investigation. **Josephine Lunaria Berboso:** Writing – review & editing, Methodology, Investigation. **Arthur Mark Richards:** Writing – review & editing, Resources, Methodology, Investigation. **Christopher Chen:** Writing – review & editing, Resources, Data curation, Conceptualization. **Saima Hilal:** Writing – review & editing,

Supervision, Resources, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100127.

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