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Vascular Health Indices and Cognitive Domain Function: Singapore Longitudinal Ageing Studies

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Abstract.
Background: Few studies have comprehensively evaluated the relationship between vascular disease and cognition of older adults without cardiac disease.
Objective: We explored the associations of structural atherosclerosis, vascular stiffness, and reactivity with global, memory, attention, language, visuospatial ability, and executive function in community-dwelling, non-demented older Asians without cardiac diseases.
Methods: Cognition was assessed by Mini-Mental State Examination (MMSE) ($n = 308$) and detailed neuropsychological tests ($n = 155$). Vascular measures included carotid intima-media thickness; aortic stiffness [carotid-femoral pulse wave velocity (CFPWV), aortic augmentation index (AI), and aortic pulse pressure (PP)]; carotid stiffness [elasticity modulus (Ep), beta index (β), arterial compliance (AC), carotid AI]; and endothelial function [reactive hyperemia index (RHI)]. Multivariable analyses controlled for potential confounding by demographics, apolipoprotein E genotype and cardiovascular risk factors.
Results: The participants' mean age was 63.0 ± 6.1 years. Inverse associations with MMSE were found for AC ($\beta = 0.128$, $p = 0.019$), Ep ($\beta = -0.151$, $p = 0.008$), β index ($\beta = -0.122$, $p = 0.029$), carotid stiffness z-score ($\beta = -0.154$, $p = 0.007$); with executive function for CFPWV ($\beta = -0.209$, $p = 0.026$), AC ($\beta = 0.214$, $p = 0.005$), Ep ($\beta = -0.160$, $p = 0.050$), β index ($\beta = -0.165$, $p = 0.041$), and both aortic ($\beta = -0.229$, $p = 0.010$) and carotid ($\beta = -0.208$, $p = 0.010$) stiffness z-scores; with verbal memory for AI ($\beta = -0.229$, $p = 0.004$) and aortic ($\beta = -0.263$, $p = 0.004$) stiffness z-score; with language for AI ($\beta = -0.155$, $p = 0.025$), aortic stiffness z-score ($\beta = -0.196$, $p = 0.011$). RHI positively correlated with visuospatial ability ($\beta = 0.195$, $p = 0.013$) and executive function ($\beta = 0.151$, $p = 0.045$).
Conclusion: The results support a link between systemic vascular health and neurocognitive function in older Asian adults. Subclinical noninvasive measures of arterial stiffness and reactivity may identify individuals vulnerable to cognitive impairment.

Keywords: Arterial stiffness, carotid intima-media thickness, cognition, endothelial function

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INTRODUCTION

Vascular health refers to the structural and functional state of the circulation, including that of the endothelium. Vascular remodeling occurs with age and is exacerbated by vascular risk factors; it is characterized by pathophysiological changes in regional and local vasculature which can be detected noninvasively. Intima-media thickness (IMT) measured at the common carotid artery (CCA) is an established surrogate of subclinical atherosclerosis, and increases up to three-fold between 20 and 90 years of age as elastin is replaced by collagen. Stiffening of the aorta, a viscoelastic conduit through which pulse waves propagate, is reliably assessed by measuring carotid-femoral pulse wave velocity (CFPWV) [1]. Greater arterial stiffness is reflected by more rapid forward wave transmission and earlier return of reflected waves from the terminal aorta [1]. As a consequence, the central aortic systolic blood pressure (SBP) increases and the diastolic blood pressure (DBP) decreases, creating an increase in central aortic pulse pressure (PP). The prematurity and quantum of these reflected waves can be quantitated by the augmentation index (AI). Local stiffness of the carotid artery can be determined from pulsatile vessel diameter changes [2]. Endothelial function includes vascular permeability, vasomotor tone, blood fluidity, and inflammatory processes which are regulated by the expression, activation, and release of nitric oxide and other bioactive substances, [3] and is traditionally assessed using brachial artery flow-mediated dilation (FMD). The clinical validity of these noninvasive metrics of structural atherosclerosis, arterial stiffness and endothelial function has been demonstrated by their ability to predict all-cause and cardiovascular mortality, acute coronary and cerebrovascular events [4–7].

The etiologic and clinical role of vasculopathy in cognitive ageing and decline, and risk of Alzheimer's disease and dementia is increasingly being investigated. Greater arterial stiffness is known to be associated with the presence of white matter hyperintensities, cerebral lacunar infarcts, and cortical atrophy of the brain [8, 9]. Several groups have reported associations with cognitive impairment and decline with increasing carotid IMT [10–15] and conduit arterial stiffness [8, 16–18]. The vast majority of studies on arterial stiffness have used PP, CFPWV, or brachial-ankle pulse wave velocity rather than direct measures of local arterial stiffness [19]. There are also no studies correlating cognition and peripheral vasodilator response as a measure of endothelial dysfunction using the novel fingertip pulse amplitude tonometry, a non-operator dependent technology.

Few studies have investigated the link between measures of vascular health to specific cognitive domains such as memory, attention, visuospatial and executive function, cognitive function being most commonly assessed globally using the Mini-Mental State Examination (MMSE). While studies evaluating the association of vascular markers with cognitive function or decline have adjusted for confounders such as demographic factors, education, depression, and vascular risks, few have controlled for heart failure which is common in older persons and known to be associated with dementia. Notably, the Framingham Offspring Cohort Study, which controlled for cardiovascular disease, including heart failure, failed to show a significant association between CFPWV or brachial reactivity with measures of logical memory and executive function [20].

In this study, we examined a population-based sample of multi-ethnic Asian adults without myocardial infarction, atrial fibrillation, or heart failure to determine the association of noninvasive measures of vascular health with cognitive performance, and specifically with memory, attention, language, visuospatial ability, and executive function. We hypothesized that indices of systemic vascular health would be related to neurocognitive function independent of established cardiovascular risk factors. Subclinical changes in indices of vascular health may therefore be "intermediate phenotypes" associated with greater likelihood of target organ damage in the brain.

MATERIALS AND METHODS

Subjects

Study participants were community-based adults identified from the second wave of the Singapore Longitudinal Ageing Study (SLAS-II), an ongoing community-based cohort study of aging and neurocognitive function among older adults in Singapore [21]. The study sample consisted of a subset of 308 participants, without a history of myocardial infarction, heart failure, or stroke, who underwent vascular profiling as control subjects in the Singapore Heart Failure Outcomes and Phenotypes (SHOP) study [22]. Importantly, none of the study participants had clinically overt dementia. The study was approved by the Institutional Review Board, National University Singapore, and all participants gave written informed consent.

Cognitive tests

MMSE

All 308 participants were assessed by the MMSE, a measure of global cognitive function with principal domains of memory, attention, language, praxis, and visuospatial ability [23]. The Chinese version of MMSE has been validated for local use among Singaporean older adults [24]. The 30 items were coded as zero if the subjects refused or were unable to complete. Total MMSE score ranges from 0 to 30, with higher score denoting better cognitive performance.

Neurocognitive tests

A comprehensive battery of neuropsychological tests was administered to a subset of 155 participants without any specific selection criteria by trained research psychologists, independent of the research nurses who administered the MMSE. The comprehensive neuropsychological test battery assessed a wide range of cognitive domains, including attention (Digit Span-Forward and Colour Trails Test 1), verbal memory (Rey Auditory Verbal Learning Test, Story Memory and Recall), language (Boston Naming Test), visuospatial ability (Brief Visuospatial Memory Test-Revised), and executive function (Digit Span-Backward, Block Design, Colour Trails Test 2 and Categorical Verbal Fluency (Animal Naming)). The assessment was administered in English, Mandarin, or Chinese dialects according to the participant's language preference. Completion of the test battery took about 1 to 1.5 h. Details of each test have been described previously [25, 26].

All raw test scores were converted into standardized Z scores, which were summed to construct five composite cognitive domain scores: Attention score = Average of ($Z_{\text{Digit Span forward longest span}} - Z_{\text{Colour Trails Test1}}$); Verbal memory score = Average of ($Z_{\text{RAVLT immediate recall}} + Z_{\text{RAVLT delayed recall}} + Z_{\text{Story Memory immediate recall}} + Z_{\text{Story Memory delayed recall}}$); Language score = $Z_{\text{Boston Naming Test}}$; Visuospatial ability score = Average of ($Z_{\text{BVMT-R immediate recall}} + Z_{\text{BVMT-R delayed recall}}$); Executive function score = $Z_{\text{Digit Span backward longest span}} + Z_{\text{Block Design}} - Z_{\text{Colour Trails Test 2}} + Z_{\text{Categorical Verbal Fluency (Animal Naming)}}$.

Carotid IMT

IMT was measured by high resolution B-mode ultrasound using a 10.5 MHz UST-5412 linear transducer and Prosound α10 system (Hitachi Aloka Medical Ltd., Tokyo, Japan) in accordance with guidelines of the American Society of Echocardiography [27]. The CCA was scanned in 3 planes (anterior, posterior and lateral) and IMT measured 1 cm proximal to the carotid bulb, in an area devoid of plaque. IMT measurements in all planes were averaged, and the mean of both right and left IMT used for analysis.

Arterial stiffness

CFPWV was measured in the supine position using applanation tonometry (SphygmoCorVx, AtCor Medical, West Ryde, NSW, Australia) [28]. The carotid-femoral path length was obtained by subtracting carotid-suprasternal notch distance measured with a tape ruler from suprasternal notch-femoral distance. Carotid-femoral transit time was obtained by subtracting the time between onset of the electrocardiographic R wave and the foot of the carotid pulse and the time between the R-wave and the femoral pulse, each averaged from 8 to 10 sequential waveforms. CFPWV was calculated as the carotid-femoral path length divided by the transit time. Left and right-sided measurements were obtained for each patient, and averaged for analysis.

From the radial artery waveform obtained by the high-fidelity tonometer, the SphygmoCorPx System reconstructed the aortic pressure waveform using a transfer function [29, 30]. This waveform depends on left ventricular ejection, as well as the timing and amount of wave reflection from branch points or areas of impedance mismatch which are determined by aortic stiffness and arteriolar tone [31]. Central or aortic AI was calculated as the increment in pressure from the first systolic shoulder of the ascending aortic pressure wave to the peak of the second, late systolic shoulder, expressed as a percentage of the pulse pressure. Aortic AI was also normalized to a heart rate of 75 bpm (AI@HR75) to facilitate comparison. Using the aortic pressure waveform, the central pulse pressure height is obtained using the values of central systolic and diastolic pressures.

Local or CCA stiffness was quantified using the eTRACKING method on a Prosound α10 ultrasound system (Hitachi Aloka Medical Limited, Tokyo, Japan) [32]. Using radio frequency signals, eTRACKING detects motion of opposed common carotid arterial walls in real-time, to 0.01 mm resolution at 10 MHz. The software ensemble-averages multiple waveforms and calculates:

(i) arterial compliance (AC) or the ratio between variations in arterial cross-sectional area and

pulse pressure, as $\pi(Ds \times Ds - Dd \times Dd) / [4(Ps - Pd)]$ where Ps = systolic BP, Pd = diastolic BP, Ds = maximum vessel diameter and Dd = minimum vessel diameter.

(ii) pressure-strain elasticity modulus (Ep) which expresses compliance relative to initial vessel diameter, as (Ps - Pd) / [(Ds - Dd)/Dd].

(iii) β index, a relatively BP-independent parameter of stiffness, as ln (Ps/Pd) / [(Ds - Dd)/Dd].

(iv) Carotid AI, similarly to aortic AI. The CCA waveform owing to proximity is modified little by the transfer function, and can be used to directly estimate aortic AI [33].

We converted all raw values of indices of carotid and aortic stiffness into standardized Z-scores, which were summed to produce two composite arterial stiffness scores: aortic stiffness z-score=average of ($Z_{Carotid\text{-}femoralPWV} + Z_{AorticAI} + Z_{AorticPP}$) and carotid stiffness z-score=average of ($Z_{Ep} + Z_{\beta\ index} + Z_{CarotidAI} - Z_{AC}$).

Endothelial function

Endothelial function was assessed using fingertip peripheral arterial tonometry (PAT) (EndoPAT2000, Itamar Medical, Caesarea, Israel) [34]. Participants were given standardized instructions on pretest preparations, which included fasting, restrictions on exercise and consumption of alcohol, coffee, tea, and cardioactive medications [35]. With the subject supine in a quiet, temperature-controlled room with hands at the level of the heart, probes with inflatable neoprene membranes and transducers were mounted on both index fingers to measure changes in digital pulse amplitude. Following the baseline recording, arterial flow in the non-dominant arm was occluded for 5 min using a rapid cuff inflation system (Hokanson E20 and AG101, D.E. Hokanson Inc., Bellevue, WA, USA) to 60 mmHg above systolic blood pressure or 200 mmHg, whichever was higher. PAT signals were recorded for at least 5 min following deflation and reactive hyperemia. A reactive hyperemia index (RHI) was calculated as the ratio of reactive hyperemic response (average amplitude of the PAT signal 90 – 150 s after cuff deflation) to basal flow (average PAT amplitude over 3.5 min), indexed to the contralateral, control arm. A RHI of $\leq$1.67 was used as the threshold value for "endothelial dysfunction".

Covariates

Socio-demographic variables included age, gender, and education. Participants were categorized by their smoking history as current or former smokers versus non-smokers. Height and weight were measured with a portable Secastadiometer (Model 708, Vogel and Halke Hamburg, Germany), with body mass index (BMI) calculated as kg/m^2. The presence of hypertension was defined by self-reported high BP, and/or a history of treatment with anti-hypertensive drugs, and/or sitting systolic BP>140 mmHg and/or diastolic BP>90 mmHg. The presence of diabetes was defined as self-reported diabetes and/or a history of treatment with oral hypoglycaemic agents or insulin, and/or fasting blood glucose $\geq$7.0 mmol/L. Dyslipidemia was defined as self-reported lipid abnormality, and/or total cholesterol $\geq$6.5 mmol/L and/or LDL-cholesterol $\geq$4.1 mmol/L and/or triglycerides $\geq$2.3 mmol/L and/or HDL-cholesterol <1.0 mmol/L and/or total cholesterol:HDL-cholesterol ratio >4.5. Apolipoprotein E (APOE) genotype was identified by polymerase chain reaction (PCR) amplification followed by restriction endonuclease digestion of the PCR product,[36] and coded based on ε4 allele carrier status.

Statistical analysis

The patients' characteristics were summarized using mean (±standard deviation) for quantitative variables and proportion (expressed as percentage) for qualitative variables. Vascular indices and markers of cognition were summarized using median (and range).

The primary analyses evaluated neurocognitive test performance as dependent variables individually for their association with markers of structural atherosclerosis, arterial stiffness, and endothelial function. Multivariable analyses were performed using multiple linear regressions in hierarchical models that controlled for potential confounding variables: (i) model 1: unadjusted; (ii) model 2: adjusted for age, gender, education, hypertension, diabetes, dyslipidemia, smoking, BMI, and APOE ε4 genotype

The results are presented as the standardized coefficients (β) and p values, with statistical significance set at $p < 0.05$ (two-tailed). All statistical analyses were carried out using SPSS software (version 15.0, SPSS Inc., Chicago, IL).

RESULTS

Characteristics of the population

Table 1 shows the demographics, clinical characteristics, and descriptive statistics for the vascular health

Table 1
Characteristics of study participants

Variable	MMSE participants ($n = 308$)	Neurocognitive domain test participants ($n = 155$)
Age, years	63.0 ± 6.1 (51–83)[1]	64.2 ± 6.4 (54–83)[1]
Female, n (%)	138 (44.8)	62 (40.0)
Ethnicity, n (%)		
Chinese	252 (81.8)	151 (97.4)
Malay	39 (12.7)	1 (0.6)
Indian	15 (4.9)	2 (1.3)
Others	2 (0.6)	1 (0.6)
Education: more than 6 y, n (%)	192 (62.3)	103 (66.5)
Hypertension, n (%)	141 (45.8)	67 (43.2)
Diabetes, n (%)	37 (12.0)	18 (11.6)
Dyslipidemia, n (%)	202 (65.6)	105 (67.7)
Current or former smoker, n (%)	76 (21.8)	35 (20.8)
Body mass index (m^2/kg)	25.0 ± 4.1 (16.3– 48.6)	24.6 ± 3.5 (17.3– 34.6)
APOE ε4 carrier, n (%)	59 (9.2)	34 (21.9)
Vascular Markers		
IMT (mm)	0.75 (0.45–1.82)[2]	0.74 (0.45–1.82)[2]
Carotid-femoral PWV	4.96 (2.55–14.10)	4.90 (2.95–13.00)
Aortic AI (%)	35.9 (6.0–65.0)	35.9 (6.0–65.0)
Aortic AI@HR75 (%)	28.2 (2.0–52.0)	27.9 (2.0–52.0)
Aortic PP (%)	51.4 (26.0–146.0)	52.4 (29.0 –98.0)
Aortic stiffness z-score	–0.029 (–1.60 – 2.26)	–0.022 (–1.66 – 2.43)
AC (mm^2/Kpa)	0.68 (0.22–1.87)	0.70 (0.22–2.18)
Ep (Kpa)	147.3 (55.0–488.0)	149.8 (55.0–488.0)
β index	10.7 (4.2–37.0)	10.9 (4.2–37.0)
Carotid AI (%)	21.5 (0.1–64.4)	21.3 (2.1– 48.5)
Carotid stiffness z-score	–0.004 (–1.96 – 3.50)	–0.002 (–1.56 – 3.00)
RHI	2.20 (0.97–3.65)	2.19 (0.97–3.65)
Cognitive tests		
MMSE total score	28.6 (17–30)	28.8 (17–30)
Attention z-score		0.027 (–2.61–2.36)
Verbal memory z-score		0.038 (–2.48–2.66)
Visuospatial ability z-score		0.012 (–2.06–1.82)
Language z-score		0.006 (–3.08 – 1.43)
Executive function z-score		0.033 (–1.60– 1.42)

APOE, Apolipoprotein E; IMT, intima-medial thickness; PWV, pulse wave velocity; AI, augmentation index; AI@HR75, augmentation index normalized to a heart rate of 75 bpm; PP, pulse pressure; AC, arterial compliance; Ep, elastic modulus; β, beta; RHI, reactive hyperemia index; MMSE, Mini-Mental State Examination. [1]Mean±SD; range in parentheses (for all such values). [2]Median; range in parentheses (for all such values).

and cognitive tests, of the study population and the subset population who underwent detailed neuropsychological tests.

Vascular health indices and MMSE

The relationships between indices of vascular health and MMSE are summarized in Table 2. Four participants had MMSE scores <23, but none had clinically overt dementia. In the unadjusted model, significant associations with MMSE were observed for IMT ($p = 0.050$) and multiple indices of arterial stiffness, including CFPWV ($p = 0.001$), AI@HR75 ($p = 0.006$), AC ($p = 0.006$), Ep ($p < 0.001$), and β index ($p = 0.003$), and both aortic and carotid stiffness composite z-scores ($p = 0.001$ and $p < 0.001$, respectively). Adjustment for demographics, education level, APOE ε4 genotype, and cardiovascular risk factors attenuated these relationships but the associations with AC ($p = 0.019$), Ep ($p = 0.008$), β index ($p = 0.029$), and carotid stiffness z-score ($p = 0.007$) (Fig. 1) remained significant.

Vascular Health Indices and Specific Cognitive Domains

Independent relationships between indices of vascular health and specific cognitive domains are summarized in Supplementary Table 1 and Table 3.

Attention

In the unadjusted model, attention was significantly associated with CFPWV ($p = 0.012$) and aortic PP

Table 2
Association between indices of vascular health and MMSE ($n = 308$)

		Model 1		Model 2	
		β	p	β	p
Carotid atherosclerosis	IMT	–0.112	0.050	–0.051	0.378
Aortic stiffness	Carotid-femoral PWV	–0.195	0.001	–0.086	0.160
	Aortic AI	–0.100	0.080	–0.049	0.387
	Aortic AI@HR75	–0.156	0.006	–0.100	0.095
	Aortic PP	–0.088	0.124	0.021	0.711
	Composite z-score	–0.185	0.001	–0.055	0.360
Carotid stiffness	AC	0.157	0.006	0.128	0.019
	Ep	–0.199	<0.0001	–0.151	0.008
	β index	–0.166	0.003	–0.122	0.029
	Carotid AI	–0.054	0.346	–0.017	0.756
	Composite z-score	–0.209	<0.0001	–0.154	0.007
Endothelial function	RHI	0.091	0.114	0.103	0.058

Model 1: unadjusted. Model 2: adjusted for age, gender, education, hypertension, diabetes, dyslipidemia, smoking, body mass index, and APOE $\varepsilon 4$ status. Abbreviations as in Table 1.

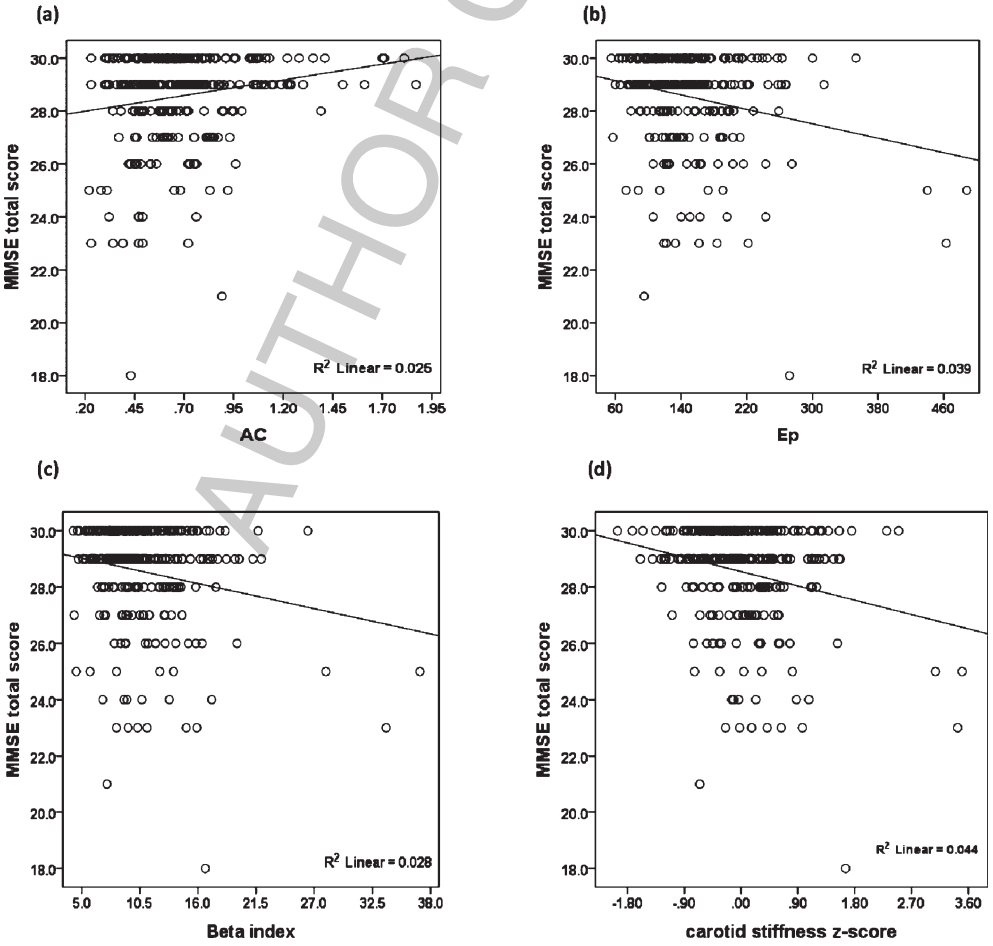

Fig. 1. Association between carotid stiffness and MMSE. Significant positive association was found for (a) AC with MMSE. Significant inverse associations were found for (b) Ep, (c) Beta index, (d) carotid stiffness z-score, with MMSE. AC, arterial compliance; Ep, elastic modulus; MMSE, Mini-Mental State Examination.

Table 3
Associations between indices of vascular health and neurocognitive specific domains ($n = 155$)

		Attention		Verbal memory		Language		Visuospatial ability		Executive function	
		β	p	β	p	β	p	β	p	β	p
Carotid atherosclerosis	IMT	0.001	0.989	–0.038	0.648	–0.047	0.511	–0.021	0.807	–0.133	0.106
Aortic stiffness	Carotid-femoral PWV	0.011	0.908	–0.084	0.398	–0.134	0.110	0.167	0.098	–0.209	0.026
	Aortic AI	0.045	0.564	–0.229	0.004	–0.155	0.025	–0.044	0.600	–0.103	0.194
	Aortic AI@HR75	0.093	0.262	–0.215	0.012	–0.157	0.030	–0.030	0.728	–0.068	0.418
	Aortic PP	–0.030	0.716	–0.160	0.065	–0.086	0.245	0.005	0.955	–0.137	0.103
	Composite z-score	0.015	0.864	–0.263	0.004	–0.196	0.011	0.041	0.662	–0.229	0.010
Carotid stiffness	AC	0.010	0.898	0.121	0.128	0.057	0.404	0.082	0.308	0.214	0.005
	Ep	0.066	0.398	–0.149	0.070	–0.061	0.389	–0.006	0.944	–0.160	0.050
	β index	0.051	0.516	–0.145	0.076	–0.058	0.409	–0.050	0.540	–0.165	0.041
	Carotid AI	0.064	0.407	0.014	0.861	–0.028	0.685	0.121	0.137	–0.023	0.770
	Composite z-score	0.062	0.430	–0.146	0.076	–0.074	0.294	–0.005	0.949	–0.208	0.010
Endothelial function	RHI	–0.006	0.939	0.089	0.259	0.047	0.482	0.195	0.013	0.151	0.045

Adjusted for age, gender, education, hypertension, diabetes, dyslipidemia, smoking, body mass index, and APOE ε4 status. Abbreviations as in Table 1.

($p = 0.007$), and aortic stiffness z-score ($p = 0.006$), but not after adjustment for other covariates (Table 3).

Verbal memory

Several indices of arterial stiffness were inversely associated with verbal memory, including carotid-femoral PWV ($p = 0.013$), aortic AI ($p = 0.004$), aortic AI@HR75 ($p = 0.012$), aortic PP ($p = 0.001$), Ep ($p = 0.003$), β index ($p = 0.005$), and aortic and carotid stiffness z-scores ($p < 0.001$ and $p = 0.005$, respectively). Only aortic AI ($p = 0.004$), aortic AI@HR75 ($p = 0.012$), and aortic stiffness z-score ($p = 0.004$) remained significantly associated with verbal memory after adjustment for demographics, education level, APOE ε4 genotype and cardiovascular risk factors (Table 3, Fig. 2).

Language

In the unadjusted model, arterial stiffness parameters that were inversely associated with language were carotid-femoral PWV ($p = 0.020$), aortic AI ($p = 0.003$) and aortic AI@HR75 ($p = 0.002$), aortic PP ($p = 0.002$), Ep ($p = 0.028$), β index ($p = 0.039$), and aortic and carotid stiffness z-scores ($p < 0.001$ and $p = 0.007$, respectively). Only aortic AI ($p = 0.025$), AI@HR75 ($p = 0.030$), and aortic stiffness z-score ($p = 0.011$) remained significantly associated with verbal memory after adjustment for demographics, education level, APOE ε4 genotype and cardiovascular risk factors (Table 3, Fig. 3).

Visuospatial ability

RHI was positively related to better visuospatial ability ($p = 0.025$) (Fig. 4) and remained significantly associated after adjustments for demographic, education, APOE ε4 genotype and cardiovascular risk variables ($p = 0.013$) (Table 3). Inverse trends were observed for aortic PP ($p = 0.071$) and β index ($p = 0.057$) in the unadjusted model.

Executive function

Carotid IMT ($p = 0.026$), arterial stiffness indices [CFPWV ($p < 0.001$), aortic PP ($p = 0.007$), AC ($p = 0.001$), Ep ($p < 0.001$), and β index ($p < 0.001$), aortic and carotid stiffness z-scores ($p < 0.001$)] and endothelial function ($p = 0.058$) were associated with executive function in the unadjusted model. CFPWV ($p = 0.026$), AC ($p = 0.005$), Ep ($p = 0.050$), β index ($p = 0.041$), aortic ($p = 0.010$), and carotid ($p = 0.010$) stiffness z-scores, and endothelial function ($p = 0.045$) remained significantly associated even after adjustment for demographics, education, APOE ε4 genotype and cardiovascular risk factors (Table 3, Fig. 5).

In further analyses, we tested for potential interactions of vascular indices with APOE ε4 in modifying the relationship between vascular health and cognition. The results showed no statistically significant interactions with APOE ε4 (data not shown).

DISCUSSION

The role of vascular disease in the pathogenesis of cognitive impairment is an area of keen investigative

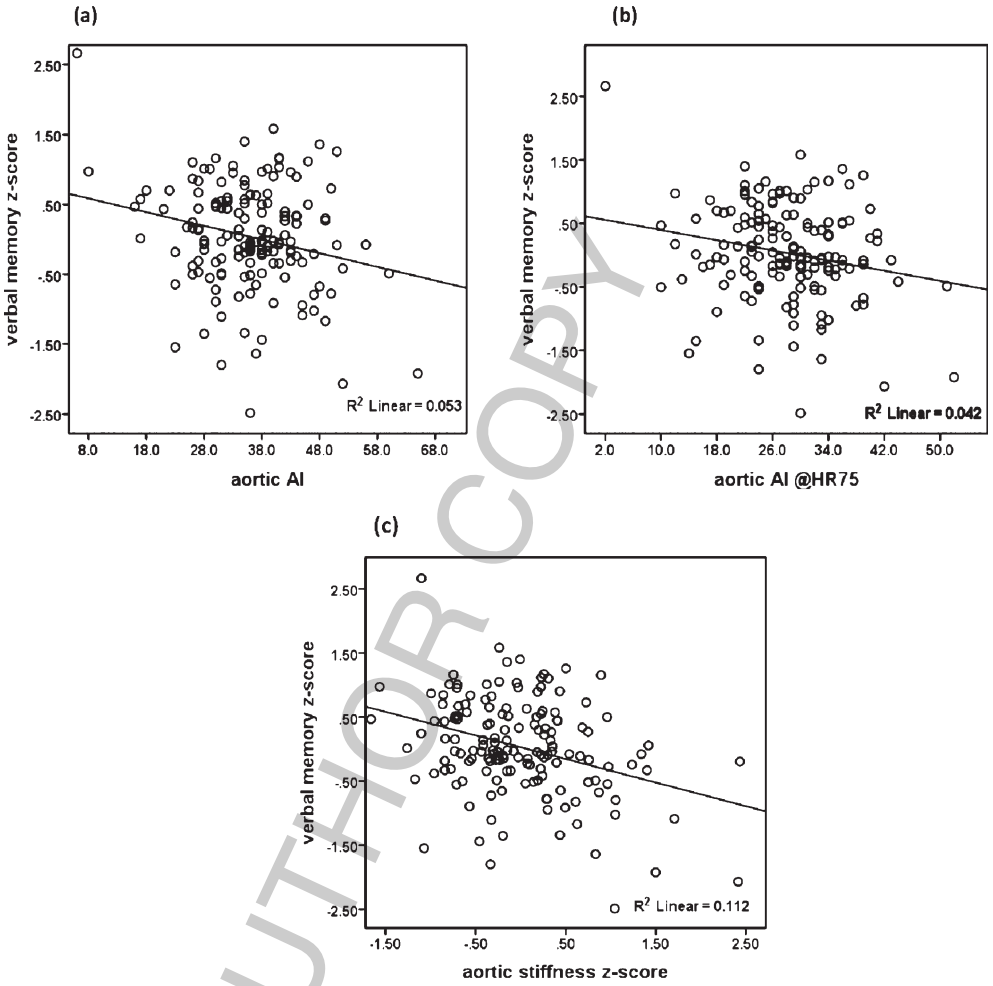

Fig. 2. Association between aortic stiffness and verbal memory. Significant inverse associations were found for (a) aortic AI, (b) aortic AI@HR75, and (c) aortic stiffness z-score, with verbal memory. AI, augmentation index; AI@HR75, augmentation index normalized to heart rate of 75 bpm.

interest. Neurodegeneration is considered to underlie most cases of dementia [37], but neuropathological studies suggest that cerebrovascular disease, either coexistent or isolated, frequently contributes to dementia among elderly community-dwellers [38]. While the precise cause-effect relationship is difficult to establish, the confluence of vasculopathy with less severe cognitive impairment and cognitive aging, arising from shared vascular risk factors, is increasingly appreciated [39, 40].

The present study represents one of few community-based studies [41–45] which have attempted to correlate multiple specific domains of cognition with subclinical vasculopathy in middle-aged to older adults. Other strengths include exclusion of subjects with a history of myocardial infarction, heart failure or other heart disease (thus eliminating a major source of confounding), comprehensive phenotyping of arterial structure, biophysical properties and responsiveness, and adjustment for the effects of psychosocial factors and vascular risk factors. Even after accounting for these confounders, we find that: (1) greater arterial stiffness was associated with impaired global cognition, verbal memory, language and executive function, and (2) "endothelial dysfunction" was associated with visuospatial ability and executive function. Our study is also the first from a multi-ethnic Asian population, and extends the implications of arterial stiffening reported in community-dwelling Japanese [46, 47] and Korean [48] elderly.

Prior studies of cognition and vascular disease have largely used measures of central (aortic) stiffness, most

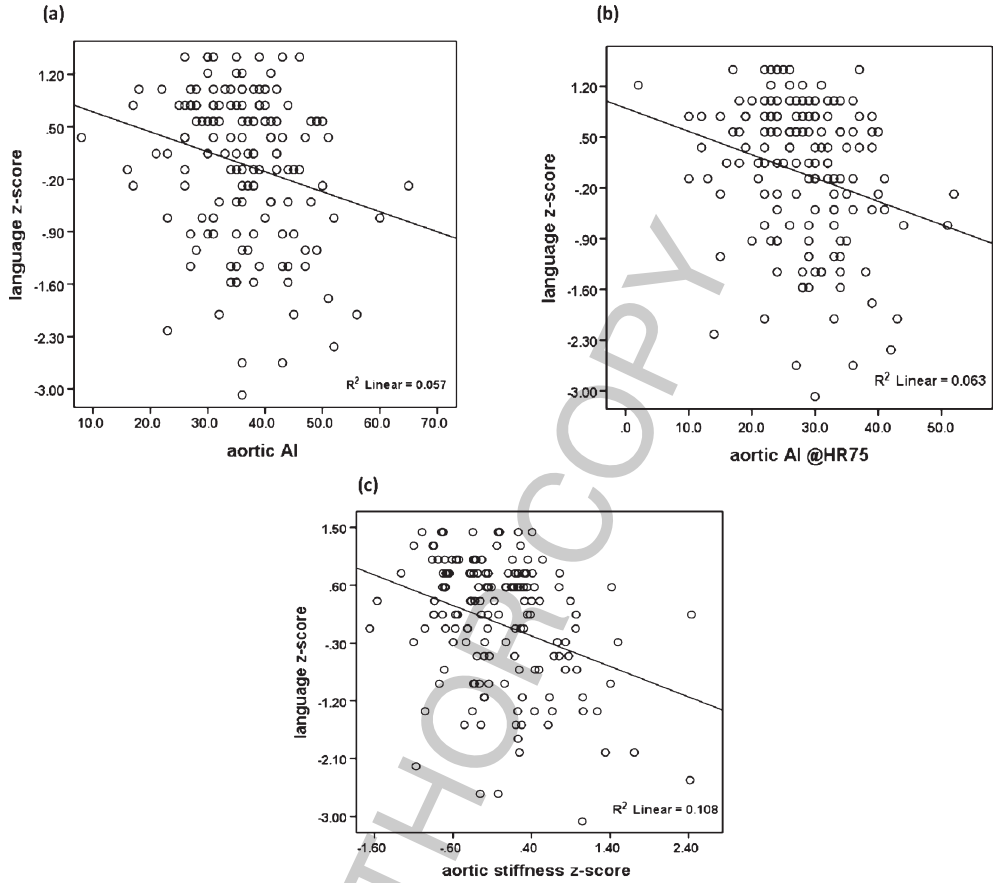

Fig. 3. Association between aortic stiffness and language. Significant inverse associations were found for (a) aortic AI, (b) aortic AI@HR75, and (c) aortic stiffness z-score, with language. Abbreviations as in Fig. 2.

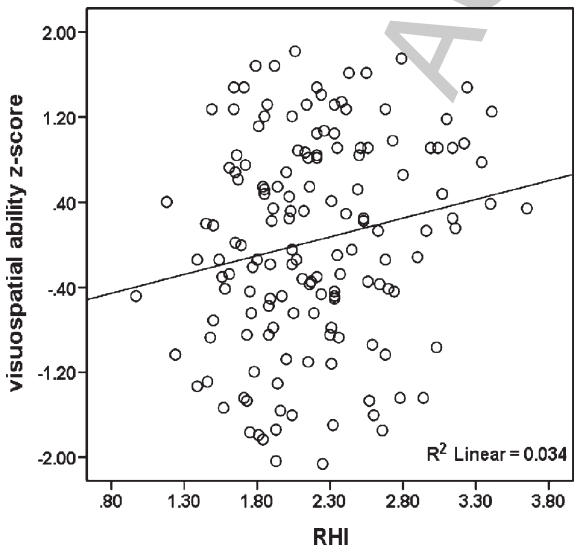

Fig. 4. Association between endothelial function and visuospatial ability. Endothelial function, measured by RHI, was positively associated with visuospatial ability. RHI, reactive hyperemia index.

commonly CFPWV (or brachial-ankle pulse wave velocity), pulse pressure, and AI. Studies evaluating their relationship with MMSE global score have mostly yielded positive associations [43, 46, 49–51] although one large population-based cohort study found no correlation [42]. The relationship with specific cognitive domains have yielded inconsistent results, but positive associations with processing speed, memory, visuospatial ability, and executive function have been variously reported [41–43, 52–55]. Our findings, that aortic AI was independently associated with verbal memory and language, and PWV with executive function, are in broad agreement with these studies. Greater arterial stiffness leads to increased arterial pulsatility, which damages the microcirculation. The high-flow, low-impedance nature of brain microcirculation renders it particularly vulnerable to such insults. The resultant injuries manifest as white matter hyperintensities, microhemorrhages, lacunar infarcts, and cerebral atrophy, pathologies which could explain the association between arterial stiffness and cognitive decline. Recent

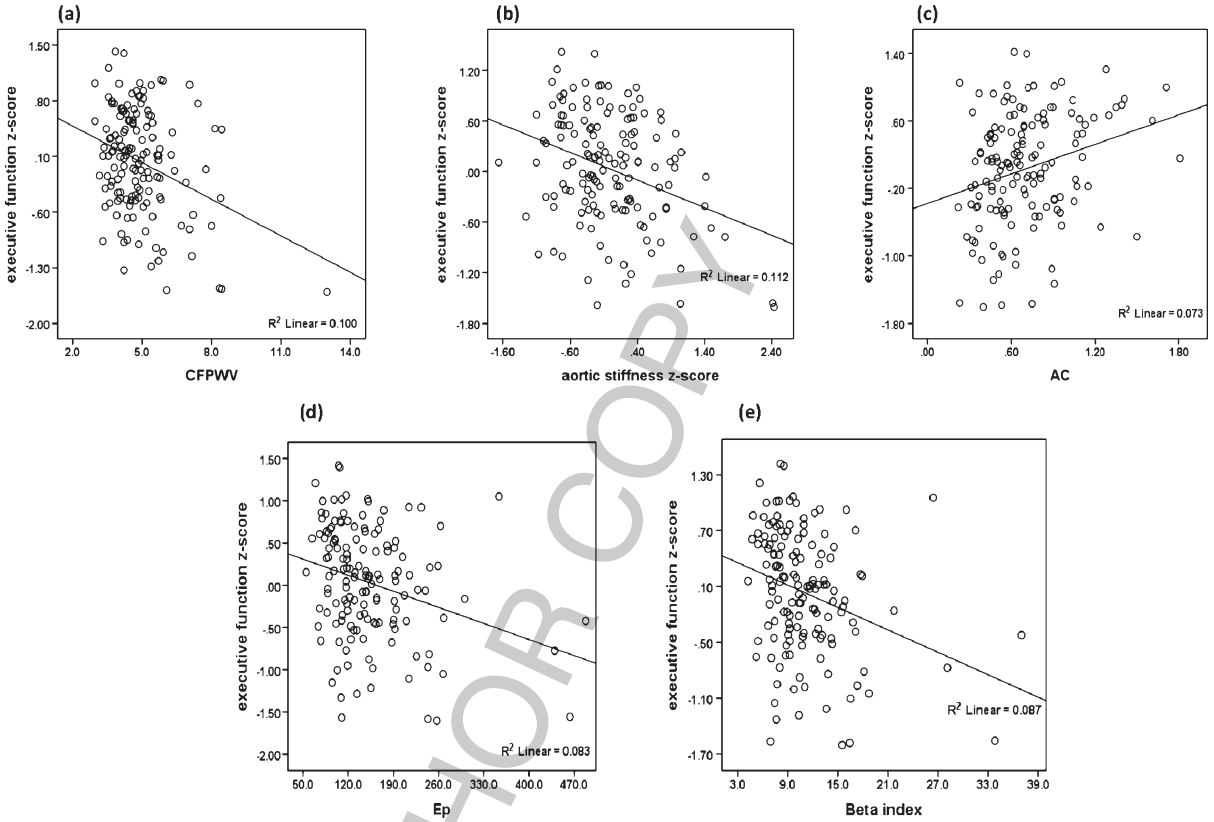

Fig. 5. Association between aortic stiffness and executive function. Significant associations were found for (a) CFPWV, (b) aortic stiffness z-score, (c) AC, (d) Ep, (e) Beta index, (f) carotid stiffness z-score, (g) RHI, with executive function. CFPWV, carotid-femoral pulse wave velocity; AC, arterial compliance; Ep, elastic modulus; RHI, reactive hyperemia index.

studies show that arterial stiffness is associated with amyloid-β deposition, independent of its association with white matter hyperintensities. Previously thought to be pathognomonic of Alzheimer's disease, cerebral amyloid-β deposition has been shown to be present in up to 34% of non-demented adults [56] and increases with age [57]. In a group of non-demented individuals, Hughes and colleagues demonstrated that arterial stiffness was associated with the extent as well as progression of amyloid-β deposition, independent of potential confounders [58]. While the exact mechanisms linking arterial stiffness and amyloid-β deposition have yet to be elucidated, their finding underscores the importance of vasculopathy in cognitive ageing and decline.

To our knowledge, only one published study has correlated a direct measure of CCA stiffness to cognitive performance. Using the same eTRACKING method, Jurasic et al [19]. found higher β index in 38 patients with dementia compared to controls but there was considerable overlap, and confounders were not controlled for. In our study, CCA AC, Ep, and β index were independently related to MMSE global cognition score and executive function, even in the absence of overt dementia. While AC, Ep, or β index were additionally associated with verbal memory and language domains in unadjusted models, they were no longer significant in multivariable analyses. Carotid AI was also not predictive in any adjusted analysis. By comparison, measures of central or conduit arterial stiffness were more robust predictors across several domains of cognitive functioning. The causes for this discrepancy are unclear but the aorta more directly bears the brunt of pressure pulsatility, increasing fragmentation of elastic lamellae and reducing compliance. Even though the aorta and CCA are elastic arteries, the aorta becomes disproportionately stiff compared to the CCA with age, especially in the presence of hypertension and diabetes [59]. Accelerated aortic stiffening in itself may predispose to resistant hypertension and its cerebrovascular consequences [60]. Disproportionate aortic stiffening can also reduce regional impedance mismatch, paradoxically lessen wave reflection at the CCA interface and increase transmission of pulsatile flow into the

CCA, damaging the cerebral microcirculation [41, 61]. Large artery thromboembolism from the CCA can lead to stroke and cognitive decline, but the atherosclerotic aorta is also a source [62], potentially jeopardizing not only the anterior but also posterior cerebral circulation, including to the hippocampus which has a central role in memory and cognition [63]. Furthermore, there could be errors in computing CCA stiffness using brachial BP owing to pressure amplification [64]. These considerations aside, our study shows that measures of aortic and CCA stiffness may contribute non-overlapping information on vascular relationships with cognitive function.

Endothelial function is a general barometer of vascular health and precedes frank atherosclerosis. Endothelial dysfunction in the cerebral circulation may promote cognitive decline since nitric oxide regulates cerebral blood flow, modulates synaptic function in the hippocampus, and influences synaptic plasticity in the striatum and cortex [65]. Endothelial function assessed by FMD has been linked to white matter hyperintensities and cognitive performance in patients diagnosed with cardiovascular disease [66], and there is increasing evidence linking the emerging vascular hypothesis and endothelial dysfunction to Alzheimer's disease [67]. In our study, RHI determined by PAT was found to be independently associated with visuospatial impairment and executive function, but not with cognitive domains of attention, verbal memory, and language. Unlike FMD, RHI quantifies the pulsatile volume changes to reactive hyperemia in small digital arteries and their microcirculation [68]. Nevertheless, these alterations in digital flow and microvascular dilatation are in part nitric oxide- and endothelium-dependent [69, 70]. Our finding that endothelial function correlates with executive functioning extends previous work by Forman and colleagues, albeit in a younger, community-dwelling Asian cohort [66]. This also is in broad agreement with the notion that the frontal-subcortical systems are more vulnerable to vascular influences. An association between endothelial function and visuospatial ability has not previously been reported, and this finding needs to be replicated in other studies.

Carotid IMT has been shown to be inversely related to cognitive performance in several studies [10–15]. We found a similar relationship between IMT and MMSE and executive function in univariate analysis but our data did not support an association with cognition, independent of age and cardiovascular risk factors. This is unsurprising given that IMT is an intermediate phenotype for early atherosclerosis and influenced by antecedents, which we rigorously controlled for. Some studies [10, 11] did not adjust for these vascular risk factors, and one large study that did also failed to establish an independent association [71]. The similarly large Atherosclerosis Risk in Communities study also found no association of carotid IMT with change in cognition over 6 years, even though IMT correlated with baseline cognitive performance [72].

In this study, only half of the entire cohort completed comprehensive neuropsychological tests. This was not the result of specific selection but rather accounted for by: 1) subjects' refusal to participate, as further testing would require 1 to 1.5 h of commitment, 2) constraint of manpower availability, and 3) exclusion due to language difficulties in a multi-racial population as translated versions were available only in Mandarin and Chinese dialects. While the possibility of some selection bias could not be excluded, we found no significant differences in vascular health indices between those who completed the neuropsychological tests and those who did not. Given the small sample size of this study, we were unable to demonstrate statistically significant interactions of vascular indices with APOE $\varepsilon 4$. The role of APOE $\varepsilon 4$ in modifying the relationship between vascular health and cognitive function is highly plausible, and should be further explored in future studies. The cross sectional design of our study is another limitation. Longitudinally designed studies are needed to ascertain if cognitive impairment and indices of vascular pathophysiology, that are common and may share mediators, are causally related. Because neuroimaging was not systematically performed in study participants, we are unable to provide direct support to the hypothesis that cognitive impairment associated with arterial stiffness and endothelial dysfunction is mediated by abnormalities of cerebral blood flow and small vessel disease.

In conclusion, our exploratory evaluation demonstrated an inverse relationship between arterial stiffness and global cognition, verbal memory, language and executive function, and endothelial dysfunction with worse visuospatial ability and executive function. The results provide further support for the vascular hypothesis of Alzheimer's disease and dementia, by demonstrating an independent link between systemic vascular health and cognitive performance even in the subclinical phases. Indices of intermediate vascular phenotype for neurocognitive disorders may therefore be useful for identifying individuals susceptible to cognitive impairment and dementia. Further evaluation of the longitudinal predictive value of these vascu-

lar health indices may improve patient selection for therapeutic interventions.

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SUPPLEMENTARY MATERIAL

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