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Associations of Arterial Stiffness and Carotid Atherosclerosis with Cerebral Small Vessel Disease in a Rural Community-Based Population

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Aims: We aimed to examine the associations of four extracranial artery indicators with cerebral small vessel disease (CSVD) and its total burden.

Methods: A total of 904 individuals aged 55–65 years old were included from the Taizhou Imaging Study. CSVD markers, including lacunes (LAC), white matter hyperintensities (WMH), cerebral microbleeds (CMB), and perivascular spaces (PVS), were rated based on brain magnetic resonance imaging. We also measured extracranial artery indices, including the brachial-ankle pulse wave velocity (baPWV), the ankle-brachial index, the carotid intima-media thickness (IMT), and carotid plaque. Linear and binary logistic regressions were adopted to test the associations among these four artery indicators and each CSVD marker when appropriate. Additionally, ordinal and multinomial logistic regressions were performed to assess the relationships between artery indicators and total CSVD score (range from 0–4 points).

Results: A total of 443 (49.0%) participants were found to have at least one of the CSVD markers, including 172 (19.0%) with WMH, 184 (20.4%) with LAC, 147 (16.3%) with CMB, and 226 (25.0%) with PVS. Increased baPWV was significantly associated with each CSVD marker, increasing carotid IMT was associated with LAC and PVS, and the presence of carotid plaque was associated with WMH volume and PVS. Moreover, per SD increment of baPWV (odds ratio [OR]: 1.29, 95% confidence interval [CI]: 1.11–1.50) and the presence of carotid plaque (OR: 1.42, 95% CI: 1.05–1.92) were significantly associated with greater total CSVD scores.

Conclusion: Increased baPWV and the presence of carotid plaque appear to be associated with total CSVD burden in rural regions in China.

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Key words: Cerebral small vessel disease, Arterial stiffness, Carotid atherosclerosis

Introduction

The term cerebral small vessel disease (CSVD) is now commonly used to describe the neuroimaging, pathogenesis, and related clinical symptoms that arise from brain microvascular injuries, which include lacunes (LAC), white matter hyperintensities (WMH), cerebral microbleeds (CMB), and perivascular spaces (PVS)[1]. Elderly men and women with CSVD are more often clinically asymptomatic, making them less likely to be aware of the insidious disease progression. Substantial evidence indicates that the development of CSVD is related to the incidences of stroke and dementia[2]. Even so, a majority of CSVD cases

detected in hospitals are incidentally found on brain magnetic resonance imaging (MRI) scans performed for other diagnostic purposes. Hence, understanding the pathogenesis of CSVD to prevent its occurrence and detecting patients with cerebral microvascular lesions at an early stage is of great significance.

The functional degradation and structural alteration of the large extracranial arteries can have a profound impact on intracranial vessels[3], particularly the distal small penetrating arteries and arterioles in the brain. Brachial-ankle pulse wave velocity (baPWV) and ankle-brachial index (ABI) are thought to reflect peripheral arterial stiffness and, in part, aortic stiffness[4, 5]. Moreover, carotid intima-media thickness (IMT) and plaque are thought to represent subclinical carotid atherosclerosis or systematic atherosclerosis[6, 7]. Several previous studies have reported these large artery related indicators to be associated with cerebrovascular diseases, especially stroke[8, 9].

However, although there is evidence supporting a link between some findings, for instance, arterial stiffness and carotid atherosclerosis, with one or more CSVD markers, to date there have been no studies investigating the associations between multiple types of arterial indicators and CSVD or its total burden in the same population. The total burden of CSVD is an emerging concept and comprehensive score which represents global cerebral small vessel injury[10].

Using the population-based Taizhou Imaging Study (TIS), we aimed to evaluate the relationships of multiple extracranial artery indictors with the prevalence or severity of radiological markers of CSVD (LAC, CMB, PVS, and WMH) as well as total CSVD burden. Through our research, we hope to provide insights into the pathogenesis of CSVD and more evidence for the study of CSVD-related risk factors.

Materials and Methods

Study Population

The participants in the present study were a part of the TIS, which is embedded within the Taizhou Longitudinal Study (TZL)[11]. Rationales and designs of the TIS have been published elsewhere[12]. In brief, we selected three villages in which local residents showed the highest response rate in the TZL survey. After excluding migrant workers, the remaining 1049 individuals without malignant tumors or cardiovascular diseases were invited to receive the TIS baseline survey. From January 2013 to September 2018, a total of 918 individuals completed sets of baseline examinations. In addition, nine participants were excluded from the current study because asymptomatic cerebral infarctions or traumatic brain injury lesions were detected, and five were excluded for poor imaging quality. These samples could not be included in statistical analysis, and we eventually conducted analyses based on 904 eligible participants (**Supplementary Fig. 1**). All study individuals provided written informed consent. The procedures followed were in accord with the latest version of the Declaration of Helsinki.

Detection of Magnetic Resonance Imaging Markers of Cerebral Small Vessel Diseases

Brain images were collected by a 3-Tesla MRI scanner (Magnetom Verio Tim scanner; Siemens, Erlangen, Germany) in Taizhou People's Hospital according to a standard protocol designed in advance. The sequences and parameters used to perform MRI have been described in detail in our previous study[13].

All subtypes of CSVD were evaluated by two senior neurological physicians according to the Standards for Reporting Vascular Changes on Neuroimaging[2]. LACs were determined as subcortical focal low-signal regions on fluid-attenuated inversion recovery (FLAIR) and T1-weighted sequences were round or ovoid, with maximum axial diameters between 3 and 15 mm. These cavity-like lesions were generally surrounded by hyperintense rims, which were distinct from PVS lesions[14]. CMBs were identified on T2*-gradient recalled echo or susceptibility weighted imaging sequences and appeared as small, round, and nearly homogeneous shapes with diameters of 2 to 5 mm. Large PVSs were distributed along with perforating vessels in areas such as the basal ganglia and centrum semiovale and appeared as cerebrospinal fluid-like signals that were visible on FLAIR sequences. Their contours mainly appeared as long strips with diameters higher than 3 mm but no larger than 20 mm.

The severity of WMH was assessed according to widely used quantitative and semi-quantitative scales. We adopted the Fazekas rating scale[15] to estimate the WMH burden in periventricular and deep regions. WMH were defined as the occurrence of moderate or severe lesions in either of these two areas (Fazekas score ≥ 2)[16]. In addition, WMH volumes were auto-

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matically segmented and evaluated via Statistical Parametric Mapping (SPM 12) software. Two neurologists who were unaware of the participants' clinical information independently implemented assessments based on magnetic resonance scanning pictures in Horos software (Version 1.1.7). If there were inconsistent diagnostic results, the image was submitted to an experienced radiologist who read the image again and made the ultimate judgment. The inter-rater agreement was high for each CSVD marker with a kappa value of 0.896 for WMH, 0.783 for LAC, 0.752 for CMB, and 0.827 for PVS.

In addition, to reflect the global underlying vascular burden in the brain, we established an incorporating and ordinal variable. The occurrence of any of the four aforementioned MRI markers was assigned a value of one point, and each sample therefore had a compound score ranging from 0 to 4 points[10, 17].

Measurement of Carotid Intima-Media Thickness and Plaque

Methods for measuring carotid IMT and plaque were described in our previous study[18]. The sonographer measured the IMT of far walls, and two segments of carotid artery 10 mm proximal and distal to the carotid bulb were taken as the optimal sites for measurement. Bilateral common and internal carotid IMT were measured and generated four records. The maximum value of these records was used for statistical analysis. Carotid plaque was determined as fulfilling any of the three following circumstances: focal protrusion into the vascular lumen exceeds 0.5 mm, 50% thicker than the surrounding IMT, or IMT >1.5 mm[19, 20]. Ultrasound examinations were performed on the same machine by the same sonographer via computerized software, and the data were captured within three cardiac cycles.

Measurement of Brachial-Ankle Pulse Wave Velocity and Ankle-Brachial Index

We measured baPWV and ABI using a fully automatic diagnostic apparatus (BP-203RPE III; OMRON-Colin, Japan)[18]. Participants underwent examinations in supine position after relaxing for 5 minutes. In the arterial segment, the distances from the central heart to the brachium and the ankle were estimated according to body height. baPWV was automatically calculated as the difference between the two paths divided by the transmission time interval of the waveform required to reach the detection points in the brachium and ankle. ABI was calculated by dividing the systolic blood pressure at the ankle by that at the brachium. Both indicators were bilaterally measured, and the mean value of left and right baPWV was used for analysis. Low ABI was defined as either side measurement ≤ 0.9, while index >1.4 was regarded as high ABI[4]. We found only one participant with a high ABI value and excluded this sample in final analysis, focusing on the associations of low ABI with CSVD markers and total CSVD score.

Covariates

Information on the characteristics of participants, including demographic data (age, sex, and years of education), lifestyle data (smoking), and medical and medication history, was collected through standardized questionnaires. Body height and weight were automatically collected by a validated instrument. Current smoking was defined as having smoked at least one cigarette every 1–3 days in the past 6 months (yes vs. no). All participants' blood pressure was measured (Omron, Ltd., Tokyo, Japan) in the right upper arm in a sitting position, after resting for 10 min in a quiet room. We measured it twice at a 5-minute interval, and the average value was used for statistical analysis. Hypertension was defined as blood pressure ≥ 140/90 mmHg, a self-reported history of hypertension, or current use of blood pressure-lowering medicines. We calculated the mean arterial pressure as two-thirds of the diastolic blood pressure plus one-third of the systolic blood pressure. Complete information concerning how to collect, transport, store, and detect fasting blood samples has been described elsewhere[12]. We also evaluated total cholesterol, triglyceride, and fasting blood glucose levels. Diabetes mellitus was defined as fasting blood glucose ≥ 7.0 mmol/L, self-reported diabetes, or current use of anti-diabetic drugs. Hyperlipidemia was defined as total cholesterol ≥ 5.2 mmol/L, triglyceride ≥ 1.7 mmol/L, a self-reported previous diagnosis, or current use of lipid-lowering medicines.

Statistical Analysis

Multivariable linear and logistic regressions were performed to investigate the independent relationships between extracranial artery indicators and four CSVD markers. Specifically, linear regression models were used to assess the associations of baPWV, IMT (continuous variables, per standard deviation [SD] increase), low ABI, and carotid plaque (presence vs. absence) with the volume of WMH. Given that the distribution of WMH volume was considerably skewed, we performed a rank transformation[21] on the data to satisfy the precondition for using linear regression analysis. Binary logistic regression models were used to determine the correlations among the four aforementioned artery indicators with LAC, CMB, and PVS. Subsequently, we carried out a stratified

Table 1. Basic features of participants

	N	Overall
General features		
Age, years	904	59.7 ± 3.0
Women	904	500 (55.3)
SBP, mmHg	902	137.7 ± 20.1
DBP, mmHg	902	82.4 ± 11.8
MAP, mmHg	902	100.8 ± 13.7
Current smoking	898	284 (31.6)
BMI, kg/m^2	904	24.2 ± 3.2
Hypertension	904	488 (54.0)
Diabetes	904	107 (11.8)
Hyperlipidemia	904	473 (52.3)
Use of antihypertensive medicines	904	272 (30.1)
Measurement of arterial indicators		
baPWV, cm/s	869	1,539.8 ± 279.2
Low ABI	869	29 (3.3%)
IMT, mm	859	0.9 ± 0.3
Plaque	894	232 (26.0)
Cerebral neuroimaging markers		
Presence of CSVD	904	443 (49.0)
LAC	904	184 (20.4)
WMH (Fazekas score ≥ 2)	904	172 (19.0)
WMH volume, mL	891	1.1 (0.5, 2.0)
CMB	903	147 (16.3)
PVS	904	226 (25.0)
CSVD group		
0		461 (51.0)
1		271 (30.0)
2		85 (9.4)
3		60 (6.6)
4		27 (3.0)

Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; BMI = body mass index; FBG = fasting blood glucose; baPWV = brachial-ankle pulse wave velocity; ABI = ankle-brachial index; IMT = intima-media thickness; LAC = lacune; WMH = white matter hyperintensity; CMB = cerebral microbleed; PVS = perivascular space; CSVD = cerebral small vessel disease.
Data listed are means ± standard deviation, frequency with percentage, or median with interquartile range.

analysis by hypertension status and sex. All analyses were performed with adjustment for age, sex, and mean arterial pressure (Model 1) and controlled for other covariates, including smoking status, current use of antihypertensive medicines, body mass index, diabetes, and hyperlipidemia[22, 23] (Model 2). Receiver operating characteristic curve analysis was applied to determine the optimal cut-off values of extracranial artery indictors for discriminating the presence or absence of CSVD.

To determine the correlations between the four artery indictors and total CSVD score, both multinomial and ordinal logistic regressions were used. Multinomial regression model was used to determine the odds ratio (OR) of various subgroups with a total CSVD score ≥ 1 toward the non-CSVD subgroup (0 points) by taking the total score as the response variable and various arterial indictors as independent variables. Moreover, ordinal regression model was applied to determine whether there was a significant trend for ORs to increase. Statistical analyses were performed using R software (Version 3.5.2), and two-side $P < 0.05$ was considered significant.

Results

The characteristics of this study population (N = 904) are listed in **Table 1**. The mean (SD) age of the

Table 2. Multivariable linear regression and binary logistic regression analyses of clinical artery indicators and MRI markers of CSVD

	LAC		WMH[§]		CMB		PVS	
	OR (95% CI)	*p*	*β* (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
baPWV, per SD increase								
Model 1	1.28 (1.06, 1.55)	0.008	0.11 (0.03, 0.18)	0.005	1.34 (1.10, 1.64)	0.003	1.33 (1.11, 1.59)	0.002
Model 2	1.26 (1.04, 1.53)	0.020	0.10 (0.02, 0.18)	0.011	1.30 (1.06, 1.60)	0.012	1.33 (1.10, 1.59)	0.003
Low ABI, presence vs. absence								
Model 1	1.45 (0.56, 3.34)	0.405	-0.14 (-0.49, 0.21)	0.443	2.18 (0.83, 5.15)	0.089	0.54 (0.16, 1.44)	0.267
Model 2	1.47 (0.57, 3.40)	0.392	-0.13 (-0.48, 0.23)	0.482	2.51 (0.94, 6.02)	0.049	0.57 (0.16, 1.51)	0.305
IMT, per SD increase								
Model 1	1.36 (1.16, 1.59)	<0.001	-0.04 (-0.11, 0.02)	0.145	1.10 (0.92, 1.30)	0.282	1.25 (1.08, 1.46)	0.003
Model 2	1.30 (1.11, 1.53)	0.001	-0.05 (-0.12, 0.01)	0.102	1.07 (0.88, 1.27)	0.474	1.23 (1.05, 1.43)	0.009
Plaque, presence vs. absence								
Model 1	1.15 (0.78, 1.67)	0.478	0.19 (0.05, 0.34)	0.009	1.05 (0.69, 1.59)	0.808	1.45 (1.02, 2.05)	0.035
Model 2	1.17 (0.79, 1.72)	0.419	0.19 (0.05, 0.34)	0.010	1.04 (0.67, 1.59)	0.866	1.48 (1.03, 2.11)	0.031

Abbreviations: baPWV = brachial-ankle pulse wave velocity; ABI = ankle-brachial index; IMT = intima-media thickness; LAC = lacune; WMH = white matter hyperintensity; CMB = cerebral microbleed; PVS = perivascular space; CSVD = cerebral small vessel disease; OR = odds ratio; SD = standard deviation; CI = confidence interval.

Model 1: adjusted for age, sex, and mean arterial pressure. Model 2: Model 1 + current smoking, use of antihypertensive medicines, body mass index, diabetes, and hyperlipidemia.

[§]WMH volume was rank transformed.

participants was 59.7 (3.0) years old, and 500 (55.3%) individuals were women. A total of 443 (49.0%) participants were categorized into the group possessing any of the four MRI markers; specifically, 271 (30.0%) were included in the 1-point group, 85 (9.4%) in the 2-point group, 60 (6.6%) in the 3-point group, and 27 (3.0%) in the 4-point group.

Table 2 summarizes the multivariable statistical analyses between arterial indicators and neuroimaging markers of CSVD. Increased baPWV was significantly associated with larger WMH volume (*β*: 0.10, 95% confidence interval [CI]: 0.02–0.18) and a higher likelihood of LAC (OR: 1.26, 95% CI: 1.04–1.53), CMB (OR: 1.30, 95% CI: 1.06–1.60), and PVS (OR: 1.33, 95% CI: 1.10–1.59). In addition, we found that a thicker intima-media layer was significantly correlated with a higher likelihood of LAC (OR: 1.30, 95% CI: 1.11–1.53) and PVS (OR: 1.23, 95% CI: 1.05–1.43). Participants with carotid plaque tended to have larger WMH volumes (*β*: 0.19, 95% CI: 0.05–0.34) and a higher likelihood of PVS (OR: 1.48, 95% CI: 1.03–2.11). No significant associations were found between low ABI and any marker of CSVD. Since baPWV was most closely related to each CSVD marker as well as total CSVD burden among all extracranial artery indices, the optimal cut-off value of baPWV for discriminating the presence of CSVD was 1,529 cm/s (sensitivity, 64.7%; specificity, 62.0%) by receiver operating characteristic curve analysis.

In the analyses stratified by hypertension status, the data displayed in **Table 3** show that hypertension may play different roles in different associations. First, the correlations between baPWV and PVS (OR: 1.28, 95% CI: 1.03–1.58 vs. OR: 1.61, 95% CI: 1.12–2.34) and between IMT and LAC (OR: 1.29, 95% CI: 1.07–1.56 vs. OR: 1.38, 95% CI: 1.00–1.88) were significant in participants with and without hypertension. Second, some of the results remained prominent in only one subgroup. For instance, among non-hypertensive individuals, increased baPWV was correlated with a higher risk of LAC (OR: 1.49, 95% CI: 1.02–2.18), and a thicker IMT was correlated with a higher risk of PVS (OR: 1.65, 95% CI: 1.23–2.26). The positive associations between baPWV with WMH volume (*β*: 0.11, 95% CI: 0.02–0.21) and the odds of CMB (OR: 1.34, 95% CI: 1.06–1.68) and the correlation between carotid plaque and WMH volume (*β*: 0.21, 95% CI: 0.00–0.41) were found only in the hypertension population. However, the significant correlation between carotid plaque and PVS disappeared in the stratification analysis. Additionally, we carried out statistical analyses stratified by sex (**Supplementary Table 1**). Interestingly, positive associations of low ABI with LAC (OR: 5.95, 95% CI: 1.56–22.96) and CMB (OR: 7.15, 95% CI: 1.60–30.24) were observed in male participants, while that of IMT with CMB (OR: 1.38, 95% CI: 1.04–1.82) were found in female participants. However, the association between plaque and PVS became no longer significant in both subgroups.

Table 3. Associations between extracranial artery indicators and MRI markers of CSVD stratified by hypertension status

		LAC		WMH[§]		CMB		PVS	
		OR (95% CI)	*p*	*β* (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Hypertension									
baPWV	Model 1	1.21 (0.97, 1.50)	0.094	0.11 (0.01, 0.20)	0.029	1.34 (1.06, 1.68)	0.012	1.24 (1.01, 1.52)	0.043
	Model 2	1.20 (0.96, 1.50)	0.111	0.11 (0.02, 0.21)	0.023	1.34 (1.06, 1.68)	0.012	1.28 (1.03, 1.58)	0.024
Low ABI	Model 1	1.96 (0.40, 8.18)	0.364	-0.34 (-1.03, 0.35)	0.333	2.83 (0.54, 13.40)	0.185	0.75 (0.11, 3.32)	0.727
	Model 2	1.89 (0.38, 7.99)	0.395	-0.33 (-1.03, 0.36)	0.340	3.63 (0.66, 18.03)	0.112	0.77 (0.11, 3.50)	0.759
IMT	Model 1	1.32 (1.10, 1.58)	0.003	-0.06 (-0.14, 0.02)	0.149	1.12 (0.92, 1.35)	0.231	1.13 (0.95, 1.34)	0.171
	Model 2	1.29 (1.07, 1.56)	0.009	-0.06 (-0.14, 0.02)	0.132	1.12 (0.91, 1.36)	0.273	1.11 (0.92, 1.33)	0.266
Plaque	Model 1	1.13 (0.71, 1.79)	0.604	0.20 (0.00, 0.39)	0.051	1.08 (0.65, 1.77)	0.754	1.33 (0.86, 2.03)	0.194
	Model 2	1.19 (0.73, 1.93)	0.470	0.21 (0.00, 0.41)	0.048	1.05 (0.63, 1.75)	0.840	1.39 (0.89, 2.18)	0.144
No Hypertension									
baPWV	Model 1	1.43 (0.98, 2.08)	0.057	0.09 (-0.04, 0.22)	0.170	1.19 (0.75, 1.81)	0.430	1.55 (1.09, 2.22)	0.016
	Model 2	1.49 (1.02, 2.18)	0.036	0.10 (-0.03, 0.23)	0.146	1.21 (0.76, 1.85)	0.393	1.61 (1.12, 2.34)	0.010
Low ABI	Model 1	1.34 (0.37, 3.80)	0.617	-0.04 (-0.43, 0.35)	0.843	2.15 (0.59, 6.25)	0.193	0.47 (0.07, 1.70)	0.325
	Model 2	1.43 (0.39, 4.12)	0.540	-0.03 (-0.43, 0.37)	0.879	2.39 (0.65, 7.10)	0.143	0.48 (0.07, 1.72)	0.329
IMT	Model 1	1.43 (1.05, 1.95)	0.022	-0.02 (-0.13, 0.10)	0.783	0.91 (0.55, 1.37)	0.692	1.65 (1.23, 2.24)	0.001
	Model 2	1.38 (1.00, 1.88)	0.044	-0.02 (-0.14, 0.09)	0.709	0.86 (0.50, 1.31)	0.527	1.65 (1.23, 2.26)	0.001
Plaque	Model 1	1.20 (0.60, 2.30)	0.596	0.20 (-0.03, 0.42)	0.082	1.04 (0.44, 2.24)	0.932	1.72 (0.93, 3.11)	0.075
	Model 2	1.24 (0.62, 2.41)	0.517	0.20 (-0.03, 0.42)	0.087	1.04 (0.44, 2.31)	0.898	1.81 (0.97, 3.28)	0.055

Abbreviations: baPWV = brachial-ankle pulse wave velocity; ABI = ankle-brachial index; IMT = intima-media thickness; LAC = lacune; WMH = white matter hyperintensity; CMB = cerebral microbleed; PVS = perivascular space; CSVD = cerebral small vessel disease; OR = odds ratio; SD = standard deviation; CI = confidence interval.

Model 1: adjusted for age, sex, and mean arterial pressure. Model 2: Model 1 + current smoking, body mass index, diabetes, and hyperlipidemia.

[§]WMH volume was rank transformed.

The findings related to baPWV (**Fig. 1**) revealed that compared with the non-CSVD group, in the CSVD group, the OR significantly increased (OR: 1.29, 95% CI: 1.11–1.50, *P* for trend = 0.001) as the total CSVD score increased. In addition, participants with carotid plaque had increased odds of having multiple markers of CSVD (OR: 1.42, 95% CI: 1.05–1.92, *P* for trend = 0.023), although this trend was not significant in the 3-point group. However, a higher IMT was associated only with higher odds of a 4-point CSVD score. There was no significant tendency for ORs to increase in either ABI or IMT (both *P* for trend > 0.05).

Discussion

In this study of a rural community-based population, we conducted a comprehensive assessment of the relationships between four extracranial artery indicators and four common MRI manifestations of CSVD as well as the total CSVD burden. Our findings revealed that regardless of the locations of cerebral microvascular lesions, increased baPWV was significantly associated with higher odds of every single MRI marker of CSVD and a more severe total CSVD burden. Moreover, an increase in carotid IMT was correlated with a higher prevalence of both LAC and PVS; and carotid plaque was correlated with larger WMH volumes and higher prevalence of PVS. These associations remained significant even after we accounted for concomitant exposure to conventional vascular risk factors. In addition, higher levels of baPWV and the presence of carotid plaque were significantly correlated with more substantial brain microvascular insults.

A previous pooled analysis summarized the evidence presented in seven cross-sectional studies and suggested that baPWV were significantly associated with CSVD markers, including WMH, CMB, and

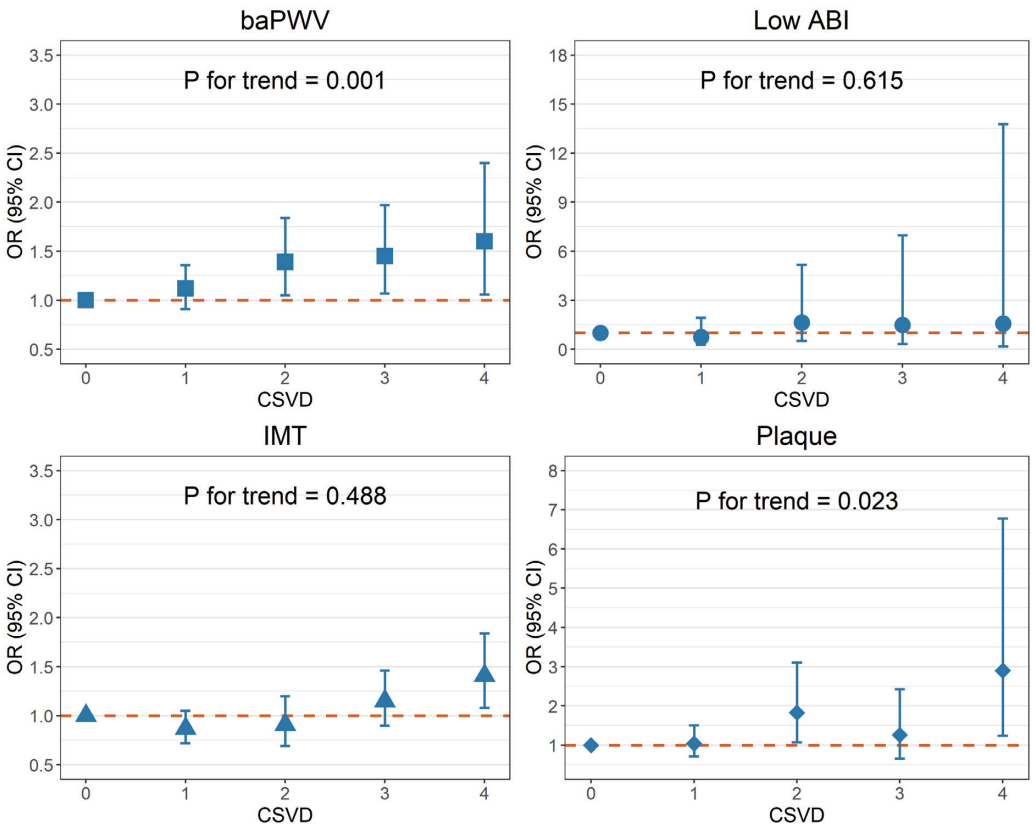

Fig. 1. Multinomial and ordinal logistic regressions of associations between four extracranial artery indicators and total CSVD score

Multinomial logistic regression was conducted to determine the ORs of each group with CSVD score ≥ 1 in comparison with the reference group (CSVD score=0). *P* for trend was generated from ordinal logistic regression using total CSVD score as an ordinal dependent variable. Two analyses corrected the same group of covariates as age, sex, mean arterial pressure, current smoking, body mass index, use of antihypertensive medicines, diabetes, and hyperlipidemia.

cerebral infarcts, after the authors accounted for demographic features and certain vascular risk factors[24]. Few studies have explored the relationship between arterial stiffness and PVS. Only Zhai *et al.*[25] found that baPWV was associated with severe PVS in white matter regions but not in the basal ganglia. Our findings expanded the evidence that a single SD increase in baPWV was associated with each CSVD marker in the same population. A stiffened aorta may exert an excessive pulsatile load and increase blood flow into brain vascular beds. Distal small vessels in the brain are highly susceptible to these impacts and will gradually generate a series of structural and functional alterations to accommodate this environment, ultimately resulting in the development of microvascular insults[26]. Furthermore, significant associations of low ABI with LAC and CMB were found in male participants, which was similar to two previous researches[27, 28]. But considering that the proportion of men with low ABI was low in this study (10/404), our findings may have been obtained by chance.

Previous studies evaluating the correlations between carotid atherosclerosis and the MRI manifestations of CSVD have shown partly inconsistent findings. The Framingham study[29] reported associations between both internal carotid IMT and severe carotid stenosis with both silent cerebral infarcts and large WMH volume. On the other hand, the 3C-Dijon Study[30] found that carotid plaque but not common carotid IMT was correlated with higher odds of lacunar infarcts and greater WMH volume. In this study, we observed significant associations between IMT and LAC, and between carotid plaque and WMH volume in total population. The features of carotid plaques usually indicate carotid artery stenosis[31, 32], which causes terminal small vessels to become chronically hypoperfused, inducing brain parenchymal ischemic lesions. Carotid IMT might be a good indicator of lacunar lesions. On the other hand, association of IMT and CMB became significant in female stratification. One of the possible explanations may be that, compared to males, IMT in females was susceptible to

cardiovascular risk factors, leading to more shared risk factors between IMT and CMB in females[33]. Few studies have explored indicators of carotid properties and PVS. Gutierrez *et al.*[34] observed that the prevalence of carotid plaque was independently correlated with PVS. In our sample, we also found an association between PVS and both carotid IMT and plaque, but the association between plaque and PVS became non-significant in stratification analysis by sex. This may indicate a confounding effect of sex that distorted the relationship. Nevertheless, previous studies have shown that a stiff aorta can produce elevated pulsatility wave transmission to the brain[25], causing damage to the integrity and function of endothelial cells[35]. In this case, increased blood-brain barrier permeability and an increase in interstitial fluid flow into surrounding spaces contributed to the formation of expanded PVS. The carotid artery is an intermediate segment in which a series of structural alterations may occur to accommodate increased blood flow and pulsatility[36]. In addition, overlapping vascular risk factors may also play a role. Further longitudinal studies are required to clarify this relationship.

A previous review suggested that hypertension may induce arterial stiffness, carotid atherosclerosis, and small artery remodeling, resulting in a closed vicious cycle[37]. Several studies have examined the relationships among arterial indicators and CSVD markers in individuals with hypertension or as subgroup analyses[38-40]. These findings have demonstrated that most of the significant associations between aortic stiffness and certain single CSVD markers are observed only in hypertensives. Hence, we attempted to provide sufficient information on the relationships of extracranial artery indicators with CSVD markers. In present study, significant associations between baPWV and WMH volume, CMB, and PVS in hypertensive patients were consistent with those presented in previous studies, except that the positive association of baPWV and LAC was significant only among non-hypertensives, indicating that in addition to blood pressure, baPWV may be a good risk stratification index. Interestingly, we also observed a significant association between baPWV and LAC in the non-hypertensive group. It is possible that because vascular risk factors were more common in hypertensive patients, the variance in the increased odds of LAC attributed to arterial stiffness was likely diluted by other factors, especially the effects from hypertension. We also noted that the association between carotid plaque and PVS was non-significant in both subgroups. Hypertension appears to distort the magnitude of the effect of carotid plaque on PVS.

We first investigated whether baPWV and carotid plaque were significantly associated with total CSVD score. The authors of previous studies proposed the establishment of a comprehensive score to represent the total CSVD burden in the brain[10]. While there is currently no evidence of associations between either arterial stiffness or carotid atherosclerosis and global cerebral microvascular insults, several recent studies have supported the feasibility of this scoring system[10, 41-43] and obtained decent results. In our dataset, multinomial and ordinal logistic regressions showed that increases in baPWV and the presence of carotid plaque were associated with significantly rising trends toward higher odds of having more MRI markers. Therefore, baPWV and carotid plaque may be potentially reliable and sensitive markers for identifying patients likely to have a high load of cerebral microvascular damage rather than a specific CSVD type, independent of the blood pressure level. Additionally, the implementation of preventive or therapeutic measures that target arterial stiffness may alleviate its effects on cerebral small vessels.

These clinical examinations were characterized by noninvasive measurements and fast completion that can reflect vascular alterations. The obtained indicators could play a pivotal role in predicting subsequent clinical events. In terms of small vessel diseases, previous studies have shown inconsistency in the relationships between carotid IMT and CSVD markers[29, 30, 44], which may due to the fact that IMT was suggestive of large vessel injury rather than small vessel lesions. Research regarding the relationships of plaque and ABI with small vessel diseases are still scarce. IMT and plaque were thought to reflect the pathological changes of carotid atherosclerosis, while baPWV and ABI suggested large artery stiffness. In this study, our findings revealed that baPWV was positively associated with four CSVD markers and total disease burden, which was in accordance with previous studies[24, 39], while others had significant associations with some CSVD markers. Therefore, we considered that baPWV may be clinically more useful in discriminating the presence of small vessel diseases. This result needs to be confirmed in other studies and populations.

From our perspective, our findings may have two clinical implications. On the one hand, CSVD has a higher prevalence among older adults worldwide, and its diagnosis relies on MRI. However, this examination is relatively costly when applied in the general population. Using indicators such as baPWV, suggesting vascular stiffness, could help discriminate high-risk populations who may need further MRI examinations. On the other hand, detecting changes in these artery markers may remind the timing of early inter-

ventions, thus reducing the incidence of asymptomatic CSVD. Several limitations of our study should be acknowledged. First, the total clinical information in the datasets collected from participants was based on cross-sectional surveys; that is, we cannot derive causality due to the nature of this observational study. Second, although we did not consider the sites and numbers of small vessel lesions in the brain during the construction of total CSVD burden scores, these scores could still reflect the overall load because the results of the total score were nearly consistent with the analyses of individual CSVD markers. Third, we did not measure carotid artery elasticity by ultrasonic technology, and further research in this regard could be interesting. Fourth, we hoped to include all the residents aged 55–65 years of three villages, but a fraction of them refused to participate, which might have led to selection bias. Nevertheless, the response rate in our study was relatively high (87.5%). The advantage of our research is that all study participants were recruited from rural communities, and this may have helped minimize loss to follow-up and make the data more reliable. In addition, we comprehensively assessed four CSVD markers and extracranial artery indicators.

Conclusion

In summary, this study suggests that an increase in baPWV is significantly correlated with higher odds of each MRI marker of CSVD, regardless of the lesion distribution, as well as with greater CSVD burden in the brain. Carotid plaque was also associated with total CSVD scores and specifically with WMH volume and PVS. These two extracranial artery indicators have the potential to be used to recognize high-risk populations who may have cerebral small vessel insults. The present results mostly apply to middle-aged individuals, and it is necessary to repeatedly verify these findings in a wider age range in the future.

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Author Contributions

Mei Cui, Xingdong Chen and Yanfeng Jiang designed this research. Kexun Zhang and Yanfeng Jiang carried out statistical analyses and wrote the initial manuscript. Li Jin and Weimin Ye supervised and provided critical comments on the manuscript. Mei Cui and Yingzhe Wang joined the process of reading the MRI images. All the authors (Kexun Zhang, Yanfeng Jiang, Yingzhe Wang, Chen Suo, Kelin Xu, Zhen Zhu, Chengkai Zhu, Genming Zhao, Li Jin, Weimin Ye, Mei Cui, and Xingdong Chen) read, amended and discussed the article.

Conflict of Interest

All authors declare that they have no conflict of interest.

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Ethical Standards

The Taizhou Imaging Study (TIS) was approved by the Ethics Committee of the School of Life Sciences, Fudan University, Shanghai, China (Institutional Review Board approval number 469).

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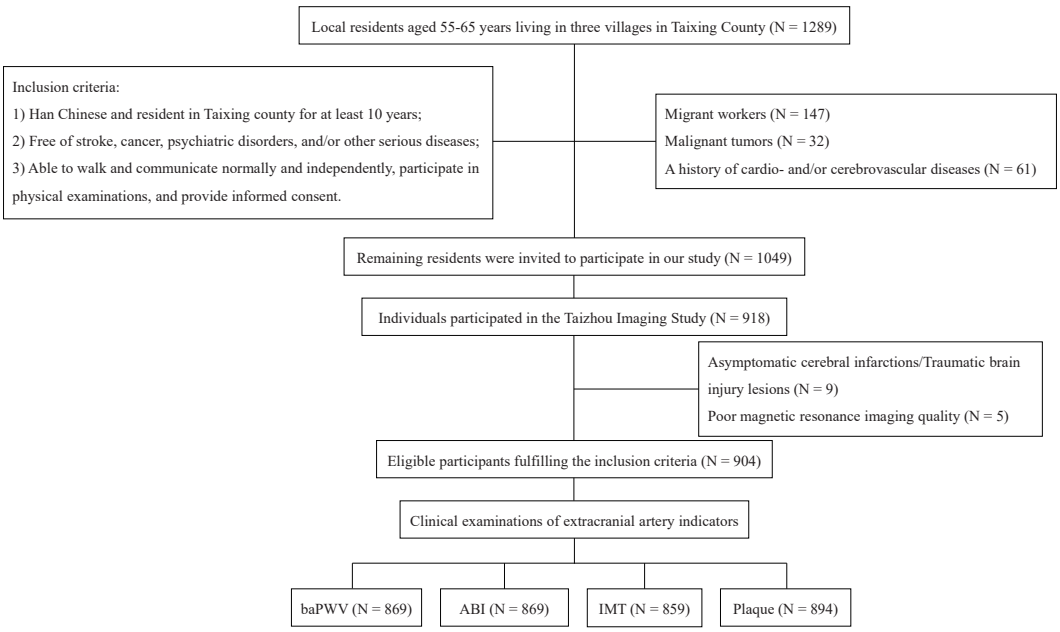

Supplementary Fig. 1. Flowchart of the participants recruitment in this study

Abbreviations: baPWV = brachial ankle pulse wave velocity; ABI = ankle brachial index; IMT = intima-media thickness.

Supplementary Table 1. Associations between extracranial artery indicators and MRI markers of CSVD stratified by sex

			LAC		WMH[§]		CMB		PVS	
			OR (95% CI)	*p*	*β* (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Males	baPWV	Model 1	1.04 (0.77, 1.37)	0.808	0.15 (0.04, 0.25)	0.007	1.27 (0.93, 1.69)	0.117	1.54 (1.19, 2.01)	0.001
		Model 2	1.02 (0.74, 1.38)	0.903	0.15 (0.04, 0.26)	0.008	1.22 (0.88, 1.67)	0.208	1.56 (1.19, 2.08)	0.001
	Low ABI	Model 1	6.05 (1.58, 23.29)	0.007	0.16 (-0.42, 0.74)	0.579	7.17 (1.66, 29.30)	0.006	NA	0.984
		Model 2	5.95 (1.56, 22.96)	0.008	0.14 (-0.43, 0.72)	0.622	7.15 (1.60, 30.24)	0.007	NA	0.984
	IMT	Model 1	1.18 (0.97, 1.43)	0.085	-0.04 (-0.12, 0.03)	0.291	0.93 (0.69, 1.18)	0.576	1.16 (0.96, 1.39)	0.111
		Model 2	1.13 (0.91, 1.39)	0.232	-0.05 (-0.12, 0.03)	0.251	0.89 (0.65, 1.14)	0.400	1.11 (0.92, 1.35)	0.265
	Plaque	Model 1	1.14 (0.66, 1.92)	0.639	0.06 (-0.13, 0.26)	0.537	1.17 (0.65, 2.10)	0.595	1.30 (0.80, 2.09)	0.287
		Model 2	1.25 (0.72, 2.16)	0.427	0.08 (-0.11, 0.28)	0.415	1.31 (0.71, 2.39)	0.385	1.36 (0.83, 2.22)	0.215
Females	baPWV	Model 1	1.57 (1.22, 2.05)	0.001	0.07 (-0.04, 0.17)	0.220	1.41 (1.07, 1.85)	0.014	1.17 (0.91, 1.50)	0.209
		Model 2	1.56 (1.19, 2.04)	0.001	0.05 (-0.06, 0.16)	0.337	1.37 (1.03, 1.81)	0.030	1.16 (0.89, 1.49)	0.265
	Low ABI	Model 1	0.47 (0.07, 1.70)	0.323	-0.30 (-0.74, 0.14)	0.183	1.04 (0.23, 3.33)	0.947	0.90 (0.25, 2.57)	0.849
		Model 2	0.51 (0.08, 1.86)	0.378	-0.25 (-0.70, 0.19)	0.264	1.27 (0.28, 4.17)	0.717	1.00 (0.27, 2.93)	0.998
	IMT	Model 1	1.72 (1.33, 2.25)	<0.001	-0.05 (-0.16, 0.06)	0.343	1.41 (1.07, 1.84)	0.012	1.45 (1.13, 1.87)	0.003
		Model 2	1.68 (1.29, 2.21)	<0.001	-0.06 (-0.17, 0.05)	0.270	1.38 (1.04, 1.82)	0.021	1.46 (1.13, 1.89)	0.004
	Plaque	Model 1	1.18 (0.67, 2.01)	0.559	0.37 (0.15, 0.59)	0.001	0.95 (0.50, 1.71)	0.868	1.64 (0.98, 2.70)	0.053
		Model 2	1.13 (0.63, 1.96)	0.668	0.36 (0.13, 0.59)	0.002	0.86 (0.44, 1.60)	0.649	1.68 (0.98, 2.82)	0.055

Abbreviations: baPWV = brachial-ankle pulse wave velocity; ABI = ankle-brachial index; IMT = intima-media thickness; LAC = lacune; WMH = white matter hyperintensity; CMB = cerebral microbleed; PVS = perivascular space; CSVD = cerebral small vessel disease; OR = odds ratio; SD = standard deviation; CI = confidence interval.

Model 1: adjusted for age, sex, and mean arterial pressure. Model 2: Model 1 + current smoking, antihypertensive drugs, body mass index, diabetes, and hyperlipidemia.

[§]WMH volume was rank transformed.