Published in final edited form as:
Int J Stroke. 2018 October ; 13(8): 832–839. doi:10.1177/1747493018784448.

Age and sex-specific associations of carotid pulsatility with small vessel disease burden in TIA and ischaemic stroke

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Abstract

Background and Purpose—Although large artery stiffness has been implicated in the pathogenesis of cerebral small vessel disease (SVD), whether carotid pulsatility, a convenient surrogate marker of arterial stiffness, is similarly associated with global burden of SVD is unknown.

Methods—We studied consecutive patients with TIA or non-disabling ischaemic stroke from the Oxford Vascular Study who had a brain MRI and carotid duplex ultrasound during 2002-2014. We determined clinical correlates of common carotid (CCA) and internal carotid artery (ICA) pulsatility index (PI) and their associations with the Total SVD Score on MRI, stratified by age (median=72).

Results—In 587 patients, CCA and ICA-PI were both independently associated with age, diabetes and premorbid mean pulse pressure after adjustment for age, sex and cardiovascular risk factors (all $p<0.05$). ICA-PI was strongly associated with SVD markers and burden, particularly lacunes, in patients aged<70 (age and sex-adjusted OR of top vs. bottom PI quartile: 5.35, 1.95-14.70, p=0.001; increasing SVD Score:2.30, 1.01-5.25, p=0.048), but not in patients aged≥70 ($p>0.05$). No associations between CCA-PI with SVD Score were noted at any age. In 94 consecutive patients who also received transcranial Doppler ultrasound, strong associations between middle cerebral artery (MCA)-PI and an increasing SVD Score was noted (unadjusted OR - MCA:4.26,1.45-12.55, p=0.009; ICA:2.37,0.81-6.87, p=0.11; CCA:1.33,0.45-3.96, p=0.61).

Conclusions—ICA and MCA-PI are associated with global SVD burden, especially in individuals aged <70 and may be causally related.

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Contributors:

KKL collected data, did the statistical analysis and interpretation, wrote and revised the manuscript. PP, SM, LL and DPJH collected data. WK provided study supervision and acquired imaging data. PMR conceived and designed the overall study, provided study supervision and funding, acquired, analysed and interpreted data, and wrote and revised the manuscript.

Declaration of interests

We declare no competing interests.

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Indexing terms

carotid pulsatility; small vessel disease; lacunes; stroke; transient ischaemic attack

Introduction

Cerebral small vessel disease (SVD) accounts for approximately 20% of all strokes and up to half of all dementias.1 However, although hypertension is one of the main risk factors leading to SVD, the pathogenesis of SVD is not fully understood.1

Stiffening of the large vessels has been associated with hypertension and with the pathogenesis of cerebral SVD.2–10 Previous studies have demonstrated that large artery stiffness is associated with silent cerebral infarcts,4, 5, 7 cerebral microbleeds,6 white matter hyperintensity (WMH)3–5, 7, 8 and strokes of lacunar subtype.10 Furthermore, stiffness of the aorta is associated with an increased arterial pulsatility measured at the common carotid artery (CCA)3, 10 and middle cerebral artery (MCA).9, 11 Studies have also shown that MCA pulsatility is correlated with leukoaraiosis,9 suggesting that leukoaraiosis and lacunar infarcts may result partly from increased arterial pulsatility transmitted to the cerebral vessels secondary to large artery stiffness.2–5, 8, 9

However, causation is uncertain. The burden of leukoaraiosis varies with age and sex, being more severe in women than in men at older ages,12 and could be due to differences in pulsatility. Sex differences are also seen in the carotid bifurcation and internal carotid artery (ICA) anatomy with the ICA/CCA ratio and ICA/external carotid artery ratio being greater in women compared with men.13 Moreover, large inter- and intraindividual variations in carotid bifurcation anatomy exist14 and could account for some unexplained susceptibility to developing SVD at an individual level. These individual and sex differences in carotid anatomy could influence associations between carotid pulsatility and global SVD burden. If so, one might expect to see stronger associations between ICA pulsatility with SVD than with CCA pulsatility.

We therefore investigated the age and sex-specific associations of ICA versus CCA pulsatility with individual neuroimaging markers and global burden of SVD (Total SVD Score) in patients with transient ischaemic attack (TIA) or ischaemic stroke, nested in the population-based Oxford Vascular Study (OXVASC). In a subset of patients, we also compared the relationships of carotid artery and MCA pulsatility with the Total SVD Score.

Methods

We prospectively studied patients with TIA or non-disabling ischaemic stroke from OXVASC. In brief, OXVASC is an on-going population-based study of all acute vascular events occurring within a population of 92728 individuals, irrespective of age, who are registered with 100 general practitioners in nine general practices of Oxfordshire, UK.15 The analysis herein includes 606 cases of TIA/ischaemic stroke recruited from November 1, 2004 to September 30, 2014 who had a cerebral magnetic resonance imaging (MRI) and also a carotid duplex ultrasound. The imaging protocol of OXVASC has been described

elsewhere.16, 17 Briefly, from April 1, 2002 - March 31, 2010 (phase 1), non-contrast CT brain and carotid duplex ultrasound were the first-line investigations and MRI and MR angiography was performed in selected patients when clinically indicated. From April 1, 2010 onwards (phase 2), brain MRI and MR angiography became the first-line imaging methods. However, carotid duplex ultrasound was also performed in selected patients in instances where MRI was contraindicated, MR angiography was not available or if carotid stenosis was identified on MR angiography and required more accurate quantification of stenosis via ultrasonography. At the end of the study period, 94 consecutive patients also received a transcranial Doppler (TCD) ultrasound upon ascertainment.

We collected demographic data, atherosclerotic risk factors, details of hospitalisation of index event during face-to-face interview and cross-referenced these with primary care records and hospital records. Cause of TIA/ischaemic stroke was classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.18 Premorbid blood pressure readings for all 606 patients during the 20 years prior to ascertainment (13404 readings in total, median number of readings per patient: 16, interquartile range [IQR]: 7-33) was also retrieved from the primary care practices and the mean systolic blood pressure, diastolic blood pressure and pulse pressure used for analysis.

Patients were scanned predominantly (488/606) with 2 scanners – Achieva, Philips Healthcare (369/443 patients who received a 1.5T MRI), and Magnetom Verio, Siemens Healthcare (119/163 patients who received a 3T MRI). Details of scan parameters are documented in Supplementary Table I. PVSs were defined as small (<3mm) punctate (if perpendicular to the plane of scan) or linear (if longitudinal to the plane of scan) hyperintensities on T2 images in the basal ganglia (BG) and centrum-semiovale (CS) based on a previously validated scale.19 Burden of PVSs were then stratified into 3 groups: <11, 11-20 and >20. The severity of subcortical and periventricular WMH was determined for each patient according to the Fazekas scale.20 Cerebral microbleeds were defined as rounded, hypodense foci up to 10mm in size and were differentiated from microbleed mimics based on current guidelines.21 The location and number of microbleeds were scored according to the Microbleed Anatomical Rating Scale.22 Lacunes were defined as rounded or ovoid lesions, >3 and <20mm in diameter, in the BG, internal capsule, CS or brainstem, of cerebrospinal fluid signal density on T2 and fluid-attenuated inversion recovery and no increased signal on diffusion weighted imaging.23 Burden of SVD was estimated by calculating the Total SVD Score where one point is allocated to each of the following: 1) presence of lacunes, 2) presence of microbleeds, 3) moderate-severe (>10) BG-PVSs and 4) severe periventricular and/or moderate-severe deep WMH.24

One neuroradiologist (WK) provided ongoing supervision of interpretation of the MRI images during the study period. Definitions of neuroimaging biomarkers were based on STRIVE.23 The intra-rater κ for 50 randomly selected scans was: lacunes - 0.85, microbleed burden (0, 1, 2-4, ≥5) – 0.88, periventricular WMH burden (Fazekas grade 0, 1, 2, 3) – 0.75; subcortical WMH burden (Fazekas grade 0, 1, 2, 3) WMH burden – 0.80 and PVS burden (<11, 11-20, >20) - 0.86 (BG) and 0.84 (CS).

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Carotid duplex ultrasound scans were performed at the Vascular Laboratory, Oxford Regional Vascular Unit of John Radcliffe Hospital, Oxford, according to current guidelines.25 The ultrasound protocol included B-mode imaging (transverse and longitudinal plane) of the proximal, mid and distal CCA, carotid bifurcation and proximal, mid and distal extracranial ICA. Presence of carotid plaques and plaque morphology were documented. Peak systolic velocity (PSV) and end-diastolic velocity (EDV) were measured by pulsed-wave Doppler analysis on the CCA and extracranial ICA bilaterally. In a subgroup of patients, intracranial vessels were examined by means of TCD sonography (DopplerBox, Compumedics DWL, Singen, Germany). MCA blood flow velocities were recorded with a handheld 2MHz probe through temporal bone window at the depth that provided the best signal. Each session was stored in the hard disc of the TCD device for subsequent off-line analysis.26 PI was calculated according to Gosling's pulsatility index as the (peak systolic velocity – end-diastolic velocity)/mean flow velocity for the explored extracranial and intracranial arteries (CCA, ICA and MCA).27

Patients gave written informed consent after an event or assent was obtained from relatives for patients who were unable to provide consent. OXVASC was approved by the local research ethics committee.

Statistical analysis

The mean CCA, ICA and MCA-PI of the left and right carotid or cerebral arteries were used for analysis if neither artery had >50% stenosis. In patients who had unilateral >50% stenosis of the CCA, ICA or MCA, the contralateral CCA, ICA or MCA-PI were used for analysis. Patients were excluded from the main analysis if they had bilateral >50% stenosis of the CCA, ICA and/or MCA.

We determined the clinical predictors of CCA and ICA-PI by linear regression in a univariate model, model adjusted for age and sex as well as a multi-variate model adjusted for all co-variates (age, sex, vascular risk factors, glomerular filtration rate, and premorbid mean systolic blood pressure, diastolic blood pressure and pulse pressure). We also determined, by ordinal regression, the odds ratios (OR) of lacunes, an increasing burden of subcortical and periventricular WMH (Fazekas grade 0, 1, 2, 3), cerebral microbleeds (0, 1, 2-4, ≥5), BG and CS-PVSs (<11, 11-20, ≥20) and Total SVD Score (0, 1, 2, 3, 4) in patients with the top CCA or ICA-PI quartile, compared with those in the bottom CCA or ICA-PI quartile as reference, in an analysis stratified by median age (<70 vs. ≥70) and by sex. In the 94/606 patients who also had TCD ultrasound performed and with satisfactory bone window, we similarly determined by ordinal regression the ORs of an increasing Total SVD Score in patients with the top MCA-PI quartile, compared with those in the bottom quartile as reference.

All analyses were done with SPSS version 22.

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Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

A total of 606 patients with TIA or non-disabling stroke had a MRI and carotid Doppler ultrasound during the study period. After excluding 29 patients who had bilateral CCA or ICA stenosis >50%, 587 patients (306 TIA, 281 ischemic stroke) were included in the final analysis. Carotid Doppler ultrasound was performed on a median of 2 days (IQR 0-6) after TIA/ischaemic stroke presentation. Baseline clinical and imaging characteristics of patients are shown in Table 1. The mean (SD) age of the population was 70 (14) years and 51% were males. Lacunes were present in 20.4% of the study population, 15.7% had microbleeds, 11.2% with Fazekas grade 3 subcortical WMH, 10.9% with Fazekas grade 3 periventricular WMH, 20.8% with >20 BG-PVSs and 42.9% with >20 CS-PVSs (Table 1). The mean (SD) Total SVD Score was 1.16 (1.17). The mean (SD) CCA-PI was 1.57 (0.29), mean ICA-PI was 1.28 (0.27) and mean MCA-PI was 1.08 (0.24).

After adjusting for age, sex, vascular risk factors and premorbid blood pressure, age, diabetes and premorbid mean pulse pressure were identified as independent predictors of CCA-PI (Table 2). Male sex was associated with an increasing CCA-PI (0.119, 0.074-0.164, p<0.0001). However, this relationship was lost for ICA-PI (p=0.40) (Table 2).

We studied the associations between CCA and ICA-PI with an increasing burden of individual neuroimaging markers of SVD and global burden of SVD stratified by age (Table 3). In the 261/587 patients aged<70, significant associations between ICA-PI with lacunes (5.35, 1.95-14.70, p=0.001), increasing burden of periventricular WMH (2.86, 1.26-6.46, p=0.012), BG-PVSs (2.83, 1.07-7.46, p=0.035) and Total SVD Score (2.30, 1.01-5.25, p=0.048) was noted, even after adjusting for age and sex. However, there were no relationships between ICA-PI with neuroimaging markers of SVD in the 326/587 patients aged ≥70 (Total SVD Score – ICA: 1.20, 0.59-2.42, p=0.62) (Table 3). No relationships between CCA-PI with Total SVD Score were noted in patients aged <70 (1.08, 0.52-2.25, p=0.84) or ≥70 (1.20, 0.66-2.21, p=0.55) (Table 3). We also noted no sex-differences in between CCA-PI and ICA-PI with neuroimaging markers of SVD in men (Total SVD Score – CCA: 1.84, 1.01-3.35, p=0.046; ICA: 3.72, 2.01-6.88, p<0.0001) and women (CCA: 3.12, 1.67-5.82, p=0.0004, p_{het}=0.23; ICA: 6.06, 3.20-11.47, p<0.0001; p_{het}=0.28) (Table 4).

In 94 consecutive patients who also had a TCD ultrasound performed, we noted stronger univariate associations between MCA-PI and ICA-PI (B 0.499, 0.341-0.657, p<0.0001) than between MCA-PI and CCA-PI (0.353, 0.193-0.512, p<0.0001). Risk associations with Total SVD Score increased progressively when arteries in closer proximity to the brain parenchyma were imaged (unadjusted OR of top vs. bottom quartile of PI – CCA: 1.33, 0.45-3.96, p=0.61; ICA: 2.37, 0.81-6.87, p=0.11; MCA: 4.26, 1.45-12.55, p=0.008).

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However, due to the small number of patients who had TCD ultrasound performed, this analysis was underpowered and we did not adjust for confounding factors.

Discussion

In patients with TIA or non-disabling ischaemic stroke, we demonstrated significant age-specific associations between ICA-PI with neuroimaging markers of SVD. In patients aged<70, ICA-PI was most significantly associated with lacunes, but associations were also noted between ICA-PI with periventricular WMH and BG-PVS burden, as well as the overall burden of SVD. However, no associations between neuroimaging markers of SVD and ICA-PI were noted in patients aged ≥70. We also demonstrated that the overall associations between PI and SVD burden were in general stronger with more distal arterial beds, and that in a subset of individuals, SVD burden appeared most strongly associated with MCA-PI, followed by ICA-PI and then CCA-PI.

A number of previous studies have demonstrated that PI, measured at the CCA or MCA is a reflection of underlying large artery stiffness.9–11 Our results support these findings, as age, diabetes and premorbid pulse pressure, all of which have previously been associated with arterial stiffness,28–30 were noted to be independent predictors of CCA and ICA-PI in our study. Male sex was also a strong independent predictor of CCA-PI, but we did not note any associations between ICA-PI and sex on univariate analysis (p=0.40). These observations may be due to the underlying sex differences in carotid bifurcation and ICA anatomy, as although men may have larger CCA and ICA lumen sizes compared with women, the ICA/CCA ratio and ICA/external carotid artery ratio have been noted to be greater in women compared with men.13 However, despite known sex-differences in carotid anatomy, we were not able to delineate any significant sex differences in risk associations between CCA and ICA-PI with SVD burden.

In common with previous studies that have noted associations between large artery stiffness or arterial pulsatility with leukoaraiosis,3–5, 7–9 there were significant associations between ICA-PI with periventricular WMH burden in all patients. However, we also found significant age-specific associations between carotid PI and SVD, such that in younger individuals age <70, additional associations between ICA-PI with lacunes, BG-PVS and global SVD burden were present, but these associations were attenuated in patients aged ≥70. Age is perhaps the most important independent predictor of arterial stiffness28 and cerebral SVD,16, 31 and hence any associations between carotid PI and SVD burden would be confounded by age.

In a small subgroup of consecutive patients who also had TCD ultrasound performed, we noted that the association between PI and SVD burden appeared to increase progressively with more distal arterial beds (MCA>ICA>CCA). Together with findings from previous studies,3–5, 8, 9 our results support the hypothesis that arterial stiffening results in an increased pulsatile flow that is propagated distally, along the large arterial beds, and is subsequently transmitted to the cerebral small vessels.2–5, 8 This process may then result in the various parenchymal lesions as a consequence of cerebral SVD (e.g. leukoaraiosis, lacunes and BG-PVSs), possibly due to cerebrovascular endothelial failure, blood brain barrier dysfunction, alterations in perfusion during diastole, increased endothelial shear

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stress and/or impaired cerebral autoregulation.1, 2 However, it is uncertain how much MCA-PI is also a measure of the resistance characteristics of the distal small vessel vascular bed, and hence how much the MCA-PI risk association is due to reverse causation is unknown.

Our study has a number of limitations. Firstly, the series of patients who received a TCD ultrasound was small and although our findings have been consistent with those from other studies,6, 7, 9–11 our results would need to be confirmed in larger cohorts. Second, in contrast to previous studies,6 we were not able to demonstrate significant associations between carotid pulsatility and cerebral microbleed burden. Cerebral microbleeds could be secondary to hypertensive or cerebral amyloid angiopathy. Our cohort however, lacked power to determine whether carotid PI was a stronger predictor of strictly deep-seated microbleeds (i.e. suggestive of hypertensive angiopathy, only 7/587 patients with strictly deep microbleeds in our cohort) or strictly lobar microbleeds (suggestive of cerebral amyloid angiopathy, 44/587 patients with strictly lobar microbleeds in our cohort). Third, although we demonstrated that ICA and MCA-PI may be surrogate markers of underlying SVD burden, their prognostic value over and above traditional vascular risk factors or neuroimaging findings in patients with TIA/ischaemic stroke remains uncertain. Similarly, whether ICA or MCA-PI are able to predict progression of SVD burden was not studied in our cohort. Finally, our cohort spanned a 10-year period, during which the neuroimaging protocol of OXVASC has changed. However, when we stratified our analyses by MRI scanner, we noted similar associations between CCA and ICA-PI with Total SVD Score with no heterogeneity (CCA: p_{het}=0.16, ICA: p_{het}=0.090). Similarly, we have recently shown in our cohort that the prognostic value for recurrent stroke of individual neuroimaging markers of SVD, such as PVSs,16 as well as the Total SVD Score17 were robust to the variations in scanner type and sequences used in our study.

In conclusion, our findings suggest that ICA-PI and MCA-PI are surrogate markers of large artery stiffness and underlying SVD burden and support the hypothesis that stiffening of the large arteries results in increased transmission of pulsatile flow along the carotid and cerebral arteries and may play a role in the pathophysiology of cerebral SVD. More research is required to determine how much MCA-PI reflects input pressure or flow characteristics as compared with distal resistance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We are grateful to all the staff in the general practices that collaborated in the Oxford Vascular Study: Abingdon Surgery, Stert St, Abingdon; Malthouse Surgery, Abingdon; Marcham Road Family Health Centre, Abingdon; The Health Centre, Berinsfield; Key Medical Practice; Kidlington; 19 Beaumont St, Oxford; East Oxford Health Centre, Oxford; Church Street Practice, Wantage. We also acknowledge the use of the facilities of the Acute Vascular Imaging Centre, Oxford.

Sources of Funding

The Oxford Vascular Study is funded by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC), Wellcome Trust, Wolfson Foundation, British Heart Foundation and the European Union's Horizon 2020 programme (grant 666881, SVDs@target). Professor Rothwell is in receipt of a NIHR Senior

Investigator award. KKL is funded by a University of Oxford Croucher Scholarship. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

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Table 1
Clinical and imaging characteristics of the study population

	N=587 (TIA N=306, ischaemic stroke N=281)
Clinical characteristics	
Mean age, yr (SD)	69.5 (13.6)
Males (%)	300 (51.1)
Hypertension (%)	342 (58.3)
Hyperlipidaemia (%)	245 (41.7)
Diabetes (%)	85 (14.5)
Ever-smokers (%)	333 (56.7)
Atrial fibrillation (%)	81 (13.8)
Prior transient ischaemic attack / stroke (%)	133 (22.7)
Ischaemic heart disease (%)	103 (16.7)
Glomerular filtration rate, ml/min/1.73m^2	71.1 (21.4)
Imaging characteristics	
Common carotid artery pulsatility index (SD)	1.57 (0.29)
Internal carotid artery pulsatility index (SD)	1.28 (0.27)
Middle cerebral artery pulsatility index (SD) *	1.08 (0.24)
N with diffusion weighted imaging positive lesion (%)	125 (21.3)
N with basal ganglia perivascular spaces (%)	
1-10 (%)	316 (53.8)
11-20 (%)	149 (25.4)
>20(%)	122 (20.8)
N with centrum semi-ovale perivascular spaces (%)	
1-10 (%)	147 (25.0)
11-20 (%)	188 (32.0)
>20(%)	252 (42.9)
N with lacunes (%)	120 (20.4)
N with microbleeds (%)	92 (15.7)
1 microbleed (%)	42 (7.2)
2-4 microbleeds (%)	27 (4.6)
≥5 microbleeds (%)	27 (4.6)
Strictly deep microbleeds (%)	7 (1.2)
Strictly lobar microbleeds (%)	44 (7.5)
N with periventricular white matter hyperintensity (%)	
Grade 1 (%)	215 (36.6)
Grade 2 (%)	121 (20.6)
Grade 3 (%)	64 (10.9)
N with subcortical white matter hyperintensity (%)	

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	N=587 (TIA N=306, ischaemic stroke N=281)
Grade 1 (%)	198 (33.7)
Grade 2 (%)	116 (19.8)
Grade 3 (%)	66 (11.2)
Mean Total Small Vessel Disease score	1.16 (1.17)

* Middle cerebral artery pulsatility index was measured in a subset of 94/587 patients

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Table 2

Clinical predictors of common carotid and internal carotid artery pulsatility index

	Univarate B (95% CI)	p	Age and sex adjusted B (95% CI)	p	Multivariate adjusted B (95% CI)	p
Common carotid artery pulsatility index						
Age	0.005 (0.004, 0.007)	<0.0001	0.006 (0.004, 0.007)	<0.0001	0.002 (0.000, 0.004)	0.016
Male sex	0.106 (0.061, 0.152)	<0.0001	0.107 (0.063, 0.151)	<0.0001	0.119 (0.074, 0.164)	<0.0001
History of hypertension	0.021 (-0.026, 0.068)	0.38	-0.012 (-0.058, 0.034)	0.60	-0.050 (-0.105, 0.005)	0.075
Hyperlipidaemia	0.032 (-0.015, 0.079)	0.18	0.014 (-0.031, 0.059)	0.54	-0.006 (-0.054, 0.041)	0.80
Diabetes	0.095 (0.030, 0.161)	0.004	0.075 (0.013, 0.138)	0.018	0.079 (0.016, 0.143)	0.014
Ever-smoking	0.006 (-0.041, 0.053)	0.80	-0.008 (-0.054, 0.038)	0.74	-0.022 (-0.067, 0.022)	0.33
Atrial fibrillation	0.097 (0.031, 0.164)	0.004	0.064 (-0.001, 0.128)	0.055	0.063 (0.000, 0.127)	0.051
Glomerular filtration rate	-0.002 (-0.003, -0.001)	0.0004	-0.001 (-0.002, 0.000)	0.16	0.000 (-0.002, 0.001)	0.49
Premorbid mean SBP (per SD increase)	0.049 (0.027, 0.070)	<0.0001	0.023 (0.001, 0.046)	0.045	-0.003 (-0.061, 0.054)	0.91
Premorbid mean DBP (per SD increase)	-0.025 (-0.046, -0.003)	0.028	-0.028 (-0.049, -0.007)	0.009	-0.019 (-0.056, 0.017)	0.30
Premorbid mean PP (per SD increase)	0.081 (0.060, 0.102)	<0.0001	0.063 (0.039, 0.087)	<0.0001	0.075 (0.026, 0.124)	0.003
Internal carotid artery pulsatility index						
Age	0.008 (0.007, 0.010)	<0.0001	0.008 (0.007, 0.010)	<0.0001	0.005 (0.004, 0.007)	<0.0001
Male sex	0.019 (-0.025, 0.062)	0.40	0.020 (-0.020, 0.060)	0.32	0.025 (-0.015, 0.065)	0.22
History of hypertension	0.103 (0.059, 0.146)	<0.0001	0.051 (0.009, 0.092)	0.017	0.012 (-0.037, 0.062)	0.62
Hyperlipidaemia	0.027 (-0.017, 0.072)	0.22	0.005 (-0.035, 0.046)	0.80	-0.032 (-0.074, 0.010)	0.14
Diabetes	0.110 (0.049, 0.171)	0.0005	0.091 (0.034, 0.147)	0.002	0.098 (0.042, 0.155)	0.001
Ever-smoking	-0.008 (-0.052, 0.036)	0.72	0.004 (-0.037, 0.045)	0.86	-0.014 (-0.054, 0.026)	0.49
Atrial fibrillation	0.081 (0.018, 0.144)	0.012	0.018 (-0.041, 0.077)	0.55	0.013 (-0.044, 0.069)	0.66
Glomerular filtration rate	-0.002 (-0.003, -0.001)	<0.0001	0.000 (-0.001, 0.001)	0.72	0.001 (0.000, 0.002)	0.11
Premorbid mean SBP (per SD increase)	0.081 (0.062, 0.101)	<0.0001	0.046 (0.026, 0.066)	<0.0001	0.020 (-0.031, 0.071)	0.44
Premorbid mean DBP (per SD increase)	-0.012 (-0.032, 0.009)	0.28	-0.011 (-0.030, 0.008)	0.26	-0.024 (-0.056, 0.009)	0.16
Premorbid mean PP (per SD increase)	0.110 (0.091, 0.128)	<0.0001	0.076 (0.055, 0.097)	<0.0001	0.063 (0.020, 0.107)	0.004

CI=confidence interval; SBP=systolic blood pressure; DBP=diastolic blood pressure; PP=pulse pressure

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Table 3

Relationships of common carotid and internal carotid artery pulsatility index with individual neuroimaging markers and global burden of small vessel disease, stratified by age

	Age <70 (n=261)				Age ≥70 (n=326)			
	Univariate OR (95% CI)*	p	Age and sex adjusted OR (95% CI)*	p	Univariate OR (95% CI)*	p	Age and sex adjusted OR (95% CI)*	p
Lacunes								
CCA-PI	1.68 (0.70-4.04)	0.25	1.43 (0.57-3.55)	0.45	1.03 (0.47-2.28)	0.94	1.00 (0.45-2.25)	1.00
ICA-PI	6.17 (2.29-16.65)	0.0003	5.35 (1.95-14.70)	0.001	1.24 (0.49-3.16)	0.65	1.04 (0.40-2.73)	0.93
Subcortical WMH burden								
CCA-PI	1.55 (0.80-3.00)	0.20	1.23 (0.60-2.49)	0.58	1.30 (0.72-2.36)	0.39	1.19 (0.65-2.18)	0.58
ICA-PI	2.15 (0.99-4.65)	0.052	1.49 (0.66-3.35)	0.34	1.90 (0.96-3.78)	0.067	1.45 (0.72-2.95)	0.30
Periventricular WMH burden								
CCA-PI	1.80 (0.92-3.50)	0.084	1.40 (0.69-2.87)	0.35	1.46 (0.80-2.67)	0.22	1.30 (0.70-2.40)	0.40
ICA-PI	3.87 (1.78-8.42)	0.001	2.86 (1.26-6.46)	0.012	1.36 (0.68-2.71)	0.38	0.99 (0.49-2.02)	0.99
Cerebral microbleed burden								
CCA-PI	1.55 (0.46-5.20)	0.48	1.22 (0.35-4.25)	0.75	1.26 (0.54-2.95)	0.59	1.05 (0.44-2.49)	0.91
ICA-PI	1.50 (0.37-6.01)	0.57	1.14 (0.27-4.71)	0.86	1.99 (0.72-5.53)	0.19	1.57 (0.55-4.46)	0.40
BG-PVS burden								
CCA-PI	1.00 (0.45-2.23)	1.00	0.55 (0.23-1.32)	0.18	1.40 (0.76-2.58)	0.27	1.16 (0.62-2.16)	0.65
ICA-PI	4.25 (1.72-10.52)	0.002	2.83 (1.07-7.46)	0.035	1.57 (0.78-3.19)	0.21	0.99 (0.48-2.07)	0.98
CS-PVS burden								
CCA-PI	1.49 (0.77-2.88)	0.23	1.12 (0.56-2.23)	0.76	1.23 (0.65-2.32)	0.53	1.15 (0.60-2.19)	0.67
ICA-PI	2.71 (1.26-5.81)	0.01	1.96 (0.89-4.32)	0.095	1.67 (0.82-3.40)	0.16	1.48 (0.72-3.08)	0.29
Total Small Vessel Disease Score								
CCA-PI	1.50 (0.75-2.97)	0.25	1.08 (0.52-2.25)	0.84	1.48 (0.82-2.68)	0.19	1.20 (0.66-2.21)	0.55
ICA-PI	3.37 (1.54-7.38)	0.002	2.30 (1.01-5.25)	0.048	1.83 (0.93-3.63)	0.082	1.20 (0.59-2.42)	0.62

OR=odds ratio; CI=confidence interval; CCA=common carotid artery; ICA=internal carotid artery; PI=pulsatility index; WMH=white matter hyperintensity; BG=basal ganglia; CS=centrum semi-ovale; PVS=perivascular space

*Odds of increasing small vessel disease burden in patients in top quartile of common carotid or internal carotid artery pulsatility index compared with patients in bottom quartile as referent

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Int J Stroke. Author manuscript; available in PMC 2019 April 01.

Table 4

Relationships of common carotid and internal carotid artery pulsatility index with individual neuroimaging markers and global burden of small vessel disease, stratified by sex

	Univariate OR (95% CI)*			
	Men	**p**	**Women**	**p**
Lacunes				
CCA-PI	1.58 (0.64-3.91)	0.32	1.51 (0.70-3.27)	0.30
ICA-PI	2.99 (1.17-7.62)	0.022	2.61 (1.12-6.08)	0.026
Subcortical WMH burden				
CCA-PI	1.78 (0.97-3.23)	0.061	2.62 (1.41-4.89)	0.002
ICA-PI	3.20 (1.74-5.91)	0.0002	3.97 (2.14-7.39)	<0.0001
Periventricular WMH burden				
CCA-PI	2.00 (1.10-3.65)	0.024	3.62 (1.92-6.83)	<0.0001
ICA-PI	4.44 (2.39-8.22)	<0.0001	5.30 (2.81-9.98)	<0.0001
Cerebral microbleed burden				
CCA-PI	2.22 (0.77-6.38)	0.14	1.59 (0.64-4.01)	0.33
ICA-PI	2.21 (0.94-5.21)	0.070	4.43 (1.38-14.28)	0.013
BG-PVS burden				
CCA-PI	1.42 (0.76-2.65)	0.27	3.12 (1.62-6.01)	0.001
ICA-PI	2.89 (1.48-5.65)	0.002	7.49 (3.61-15.53)	<0.0001
CS-PVS burden				
CCA-PI	1.41 (0.77-2.59)	0.27	2.82 (1.48-5.37)	0.002
ICA-PI	3.28 (1.78-6.04)	0.0001	4.03 (2.14-7.58)	<0.0001
Total Small Vessel Disease Score				
CCA-PI	1.84 (1.01-3.35)	0.046	3.12 (1.67-5.82)	0.0004
ICA-PI	3.72 (2.01-6.88)	<0.0001	6.06 (3.20-11.47)	<0.0001

OR=odds ratio; CI=confidence interval; CCA=common carotid artery; ICA=internal carotid artery; PI=pulsatility index; WMH=white matter hyperintensity; BG=basal ganglia; CS=centrum semi-ovale; PVS=perivascular space

*Odds of increasing small vessel disease burden in patients in top quartile of common carotid or internal carotid artery pulsatility index compared with patients in bottom quartile as referent