White Matter Hyperintensities

Blood Pressure, Internal Carotid Artery Flow Parameters, and Age-Related White Matter Hyperintensities

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Abstract—White matter hyperintensities (WMH) are associated with hypertension. We examined interactions among blood pressure (BP), internal carotid artery (ICA) flow velocity parameters, and WMH. We obtained BP measurements from 694 community-dwelling subjects at mean ages 69.6 (±0.8) years and again at 72.6 (±0.7) years, plus brain MRI and ICA ultrasound at age 73±1 years. Diastolic and mean BP decreased and pulse pressure increased, but systolic BP did not change between 70 and 73 years. Multiple linear regression, corrected for vascular disease and risk factors, showed that WMH at the age of 73 years were associated with history of hypertension (β=0.13; P<0.001) and with BP at the age of 70 years (systolic β=0.08, mean β=0.09, diastolic β=0.08; all P<0.05); similar but attenuated associations were seen for BP at the age of 73 years. Lower diastolic BP and higher pulse pressure were associated with higher ICA pulsatility index at the age of 73 years (diastolic BP age 70 years: standardized β=−0.24, P<0.001; pulse pressure age 70 years: β=0.19, P<0.001). WMH were associated with higher ICA pulsatility index (β=0.13; P=0.002) after adjusting for BP and correction for multiple testing. Therefore, falling diastolic BP and increased pulse pressure are associated with increased ICA pulsatility index, which in turn is associated with WMH. This suggests that hypertension and WMH may either associate indirectly because hypertension increases arterial stiffness that leads to WMH over time, or coassociate through advancing age and stiffer vessels, or both. Reducing vascular stiffness may reduce WMH progression and should be tested in randomized trials, in addition to testing antihypertensive therapy. (Hypertension. 2014;63:1011-1018.) ● Online Data Supplement

Key Words: aging ■ blood flow velocity ■ blood pressure ■ cerebrovascular disorders ■ magnetic resonance imaging

White matter hyperintensities (WMH) are indicators of cerebral small vessel disease and are implicated in the pathogenesis of cognitive impairment, stroke, and dementia. WMH are associated with hypertension and increased risk of stroke, but the mechanism through which elevated blood pressure (BP) affects the brain is unclear. Advancing age is associated with loss of elasticity in the large arteries and muscular arterioles and increased arterial stiffness. Several risk factors, particularly hypertension, contribute to the stiffness. Arterial stiffening impairs the damping of the arterial waveform in large arteries and could lead to excessive transmission of BP pulsation to the brain. Increasing stiffness of the large central arteries is associated with WMH. One explanation for the association between arterial stiffness and WMH is that arterial stiffening exposes small vessels in the brain to high pulsatility, damaging the small vessel wall. Because this cyclic variation in BP is transmitted to the brain through the internal carotid arteries (ICA), an association among BP, ICA flow parameters, and WMH might be expected. Few studies have compared BP, ICA or middle cerebral artery (MCA) blood flow velocity, and WMH. Previous studies that investigated BP and ICA or MCA velocity parameters and WMH have focused on the pulse pressure component of BP and the pulsatility index component of the Doppler MCA or ICA waveform. However, pulse pressure is determined by diastolic BP (DBP) and systolic BP (SBP), and the relative contribution of these is a function of age: in young adults, both DBP and SBP increase, whereas in the elderly SBP increases whereas DBP reduces with age.

Here, we investigated the association between BP measured longitudinally, ICA blood flow velocity parameters, and
age-related WMH in a well-characterized large community-dwelling cohort of older adults with a narrow age-range. We hypothesized that because the ICAs are the main conduits of blood to the brain, that BP must exert its effects on the brain via the ICAs and, therefore, that we should find positive associations between BP and ICA velocity parameters, and in turn between ICA velocity parameters and WMH, if indeed there is a direct relationship between high BP and WMH at older ages.

Methods

Subjects

Study participants were members of the Lothian Birth Cohort 1936 (LBC1936). They were all born in 1936, most undertook the Scottish Mental Survey of 1947, and most were living in the Lothian (Edinburgh) area of Scotland when first recruited into the LBC1936 between 2004 and 2007. At mean age of 70 years (LBC1936 wave 1), 1091 participants undertook detailed medical and cognitive assessments. Three years later (wave 2), repeat medical and cognitive assessments were conducted (n=866); in addition, at wave 2 they underwent carotid Doppler ultrasound imaging and brain MRI (n=700, protocols detailed elsewhere). Subjects provided history of ischemic heart disease, diabetes mellitus, hypertension (diagnosed or on treatment), smoking (coded here as ever smoked previously or currently), hypercholesterolemia, peripheral vascular disease, clinically evident stroke, and any other circulatory disease, and we calculated body mass index.

Written informed consent was obtained from all participants under protocols approved by the Lothian (REC 07/MRE00/58) and Scottish Multicentre (MREC/01/0/56) Research Ethics Committees; all procedures were conducted according to institutional guidelines and the Declaration of Helsinki.

BP Measurements

BP measurements were taken from the brachial artery at waves 1 and 2 by trained research nurses in a Clinical Research Facility (http://www.wtcrf.ed.ac.uk) using an Omron 705IT monitor. Three readings of SBP and DBP were taken, sitting and standing. We calculated average SBP and DBP for the 3 sittings (or standings) and pulse pressure for each wave. Brachial pulse pressure closely reflects aortic pulse pressure—of 5 measures of arterial stiffness outside the head, brachial pulse pressure showed the strongest correlation with, and explained the largest proportion of variance in, intracranial arterial stiffness. We also calculated mean BP (Equation 1).

\[ \text{Mean BP} = \frac{\text{SBP} - \text{DBP}}{3} + \text{DBP} \]

We calculated BP variability using methods proposed previously: SD, coefficient of variation (SD of successive measurements divided by their mean value), range, real variability (average absolute difference between successive measurements), and successive variation (average squared difference between successive measurements), separately for SBP and DBP (Tables S1 and S2 in the online-only Data Supplement) and for each time point using the 3 sitting (or standing) BP measurements. Note that the availability of 3 BP measurements for variability computation limits the strength of the metrics.

Carotid Doppler Ultrasound Imaging

Carotid Doppler ultrasound imaging was performed at wave 2 on a Siemens Antares Premium Color Doppler scanner (Siemens AG, Erlangen, Germany) with 7.5 MHz variable frequency probe by experienced neurovascular ultrasonographers. Blood flow velocity readings were obtained, after 25-minute rest supine with head on pillow, from the left and right common, internal and external carotid arteries, including peak systolic and end diastolic blood flow velocities from all arteries and averaged the right and left velocities. We calculated ICA mean flow velocity, pulsatility index, and resistivity index using average values of left and right ICAs in Equations 2, 3, and 4 (ICA systolic velocity and ICA end diastolic velocity). We calculated mean velocity, rather than using the machine-derived time averaged mean, to avoid inaccurate machine calculations occurring secondary to signal drop out or artifact from the velocity waveform. ICA velocity parameters, including pulsatility and resistivity indices, closely reflect intracranial arterial velocity parameters. Measuring blood velocity parameters in the ICAs avoids the problem of the ≥10% data loss because of acoustically dense skull and incorrect MCA velocity calculations because of assumed angle of insonance that occur with transcranial Doppler ultrasound.

\[ \text{Mean velocity} = \frac{\text{ICAS} - \text{ICAD}}{3} + \text{ICAD} \]

\[ \text{Pulsatility Index} = \frac{\text{ICAS} - \text{ICAD}}{\text{Mean velocity}} \]

\[ \text{Resistivity Index} = \frac{\text{ICAS} - \text{ICAD}}{\text{ICAS}} \]

Magnetic Resonance Imaging

We report the imaging findings according to the Standards for Reporting Vascular Changes in Neurodegeneration criteria. All brain MRI data were acquired at wave 2 on a 1.5T GE Signa Horizon HDx scanner (General Electric, Milwaukee, WI) with a self-shielding gradient set, maximum gradient strength 33 mT/m, and an 8-channel phased-array head coil. The image acquisition included the following: T1-weighted coronal, T2-weighted, T25-weighted, and fluid attenuated inversion recovery sagittal whole brain scans. WMH were segmented and volumes were measured using a validated multispectral image processing tool, MCMxxxVI (www.sourceforge.net/projects/birc1936). Intracranial volume was measured using the Image Edit tool in the Analyze 9.0. WMH were visually rated by an experienced, neuroradiologist on the fluid attenuated inversion recovery sagittal whole brain scans. WMH were scored separately (0–3) and then the scores combined to give a total score out of 6.

Statistical Analysis

All statistical analyses were performed using SPSS version 19 (SPSS Inc, Chicago, IL); all statistical tests being 2-tailed, and P<0.05 being considered significant. BP measures at waves 1 and 2 were compared using paired t-tests, and health conditions at waves 1 and 2 were compared using Wilcoxon rank-sum test.

Associations between BP measures, ICA blood velocity measures, and WMH were investigated using multivariate linear regression models. The covariates that are known or proposed predictors of WMH, BP, or blood velocity parameters were included in the analysis: age in days at MRI, sex, body mass index, and self-reported history of ischemic heart disease, stroke, peripheral vascular disease, other circulatory disorders, diabetes mellitus, hypertension, smoking, and hypercholesterolemia. We modeled the association among BP, ICA blood velocity parameters, and WMH in stages, each individually and then all 3 elements together. We tested associations with and without history of hypertension included in the models (to avoid overfitting) because there was little difference in the results whether hypertension was included; we report the results without hypertension as a covariate. All relevant covariates were included in the models, and multiple testing was corrected for using the false-discovery rate. We tested both WMH volume and Fazekas score and whether the associations differed between hypertensive and nonhypertensive subjects using Pearson bivariate analysis. Because WMH were not normally distributed, in sensitivity analyses, we log transformed the WMH but found no difference in the models between the raw and transformed WMH. This was
unsurprising because of our large sample size. In view of these and to simplify the interpretation of results, we report the results of the untransformed WMH.

Results

Subjects

Of the 700 subjects with brain MRI, 6 had incomplete data reducing the final sample to 694 (Table 1), mean ages 69.6±0.8 and 72.6±0.7 years for waves 1 and 2, respectively, with the same proportion of men (53%) at both waves. The proportions with vascular diagnoses increased significantly between waves 1 and 2: hypertension (37%–48.7%), ischemic heart disease (21.7%–27.3%), diabetes mellitus (6.6%–11.0%), stroke (4.4%–6.9%), hypercholesterolemia (33.3%–41.4%), peripheral vascular disease (37.5%–42.1%), and other circulatory problems (13.6%–17.6%; all \( P < 0.00 \)). There was no significant difference in body mass index between waves 1 and 2. ICA stenosis >50% was only present (on either side) in 2.9%, and internal carotid occlusion on either side in 1 patient each (0.3%).

We found similar changes from wave 1 to 2 for BP taken while sitting or standing; therefore, all subsequent analyses refer to sitting BP (data for standing available on request). There was no significant change in SBP (Table 1), but mean and DBP fell significantly (\( P < 0.001 \)) and thus pulse pressure increased significantly (\( P < 0.001 \)) from wave 1 to 2. The mean absolute WMH volume was 12.05±12.84 mm³ or 0.83±0.90% of intracranial volume. The total median and interquartile range Fazekas score was 2.0±1.0, range 0 to 6.

BP and ICA Blood Velocity Parameters

For brevity, only the summary results of the regression analyses are presented here (Figure; Table 2; Figure S1). Full results, including covariate effects, are reported in Table S3. There were numerous relatively weak associations between BP and ICA velocities, but in general, these were strongest and most consistent for lower DBP and higher ICA pulsatility index (with few associations for SBP) and for BP measured at wave 2 (results in text) than at wave 1 (Table 2). Thus, higher ICA systolic and mean velocities were associated with lower

Table 1. Descriptive Statistics for Measures of BP, Blood Velocity in the ICA, WMH Measures, Demographic, and Health Conditions

<table>
<thead>
<tr>
<th>Parameter Assessed</th>
<th>Measures</th>
<th>Wave 1 (n=1091)</th>
<th>Wave 2 (n=694)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP measures</td>
<td>Peak systolic BP, mm Hg</td>
<td>149.45 (18.96)</td>
<td>148.69 (18.95)</td>
</tr>
<tr>
<td></td>
<td>Mean BP, mm Hg</td>
<td>104.00 (11.81)</td>
<td>102.00 (11.27)*</td>
</tr>
<tr>
<td></td>
<td>End diastolic BP, mm Hg</td>
<td>81.45 (10.17)</td>
<td>78.1 (9.68)*</td>
</tr>
<tr>
<td></td>
<td>Pulse pressure, mm Hg</td>
<td>68.00 (14.91)</td>
<td>71.34 (18.94)*</td>
</tr>
<tr>
<td>Measures of blood velocity in the ICA</td>
<td>Peak systolic velocity, cm/s</td>
<td>…</td>
<td>59.91 (20.33)</td>
</tr>
<tr>
<td></td>
<td>Mean velocity, cm/s</td>
<td>…</td>
<td>32.53 (10.59)</td>
</tr>
<tr>
<td></td>
<td>End diastolic velocity, cm/s</td>
<td>…</td>
<td>18.85 (7.09)</td>
</tr>
<tr>
<td></td>
<td>Pulsatility index</td>
<td>…</td>
<td>1.27 (0.26)</td>
</tr>
<tr>
<td></td>
<td>Resistivity index</td>
<td>…</td>
<td>0.66 (0.40)</td>
</tr>
<tr>
<td>WMH and related measures</td>
<td>White matter hyperintensities volume, cm³</td>
<td>…</td>
<td>12.05 (12.84)</td>
</tr>
<tr>
<td></td>
<td>Intracranial volume, cm³</td>
<td>…</td>
<td>1450.97 (140.57)</td>
</tr>
<tr>
<td></td>
<td>Percentage of white matter lesions in ICV</td>
<td>…</td>
<td>0.83 (0.90)</td>
</tr>
<tr>
<td></td>
<td>Total Fazekas scores, median (IQR)</td>
<td>…</td>
<td>2.00 (1.00)</td>
</tr>
<tr>
<td></td>
<td>Deep Fazekas scores, median (IQR)</td>
<td>…</td>
<td>1.00 (0)</td>
</tr>
<tr>
<td></td>
<td>Periventricular Fazekas scores, median (IQR)</td>
<td>…</td>
<td>1.00 (1)</td>
</tr>
<tr>
<td>Demographic and health conditions</td>
<td>% Men</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Age in years, mean (SD)</td>
<td>69.57 (0.83)</td>
<td>72.55 (0.71)</td>
</tr>
<tr>
<td></td>
<td>Body mass index, mean (SD)</td>
<td>27.83 (4.38)</td>
<td>27.98 (4.50)</td>
</tr>
<tr>
<td></td>
<td>History of hypertension, %</td>
<td>37.10</td>
<td>48.70†</td>
</tr>
<tr>
<td></td>
<td>History of ischemic heart disease, %</td>
<td>21.70</td>
<td>27.30†</td>
</tr>
<tr>
<td></td>
<td>History of diabetes mellitus, %</td>
<td>8.60</td>
<td>11.00†</td>
</tr>
<tr>
<td></td>
<td>History of stroke, %</td>
<td>4.40</td>
<td>6.90†</td>
</tr>
<tr>
<td></td>
<td>History of smoking, %</td>
<td>…</td>
<td>56.10</td>
</tr>
<tr>
<td></td>
<td>History of hypercholesterolemia, %</td>
<td>33.30</td>
<td>41.40†</td>
</tr>
<tr>
<td></td>
<td>History of peripheral vascular diseases, %</td>
<td>37.50</td>
<td>42.10*</td>
</tr>
<tr>
<td></td>
<td>Problems with blood circulation, %</td>
<td>13.60</td>
<td>17.60*</td>
</tr>
</tbody>
</table>

*\( P < 0.05 \).
†\( P < 0.001 \).

Measures changed significantly from wave 1 to 2. BP indicates blood pressure; ICA, internal carotid artery; ICV, intracranial volume; IQR, interquartile range; and WMH, White matter hyperintensities
DBP (all $P<0.001$) and higher pulse pressure (all $P<0.004$). Higher ICA diastolic velocity was associated with lower DBP ($\beta=-0.09; P=0.024$) and lower mean BP ($\beta=-0.08; P=0.029$) but no other BP measure. Higher ICA pulsatility index was associated with higher SBP ($\beta=0.08; P=0.04$), lower DBP ($\beta=-0.19, P<0.001$), and higher pulse pressure ($\beta=0.10; P=0.008$). Higher ICA resistivity index was associated with lower DBP ($\beta=-0.18; P<0.001$) and higher pulse pressure ($\beta=0.17; P<0.001$). All the significant associations remained significant after a correction for false-discovery rate was applied. There were no associations for BP variability parameters (Table S1).

**BP Measures and WMH Measures**

Associations between BP variables and WMH were generally stronger for BP assessed at wave 1 and for Fazekas

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**Table 2. Association Between Measures of BP and ICA Blood Velocity Parameters**

<table>
<thead>
<tr>
<th>BP Measures</th>
<th>Systolic Velocity (Wave 1)</th>
<th>Mean Velocity (Wave 1)</th>
<th>Diastolic Velocity (Wave 1)</th>
<th>Pulsatility Index (Wave 1)</th>
<th>Resistivity Index (Wave 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>0.06 (0.141, 0.256)</td>
<td>0.04 (0.285, 0.407)</td>
<td>0.01 (0.76, 0.80)</td>
<td>0.04 (0.335, 0.447)</td>
<td>0.04 (0.256, 0.394)</td>
</tr>
<tr>
<td>Mean BP</td>
<td>-0.04 (0.245, 0.394)</td>
<td>-0.02 (0.647, 0.711)</td>
<td>0.02 (0.533, 0.627)</td>
<td>-0.11 (0.003, 0.009)*</td>
<td>-0.08 (0.054, 0.111)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-0.13 (0.001,0.003)*</td>
<td>-0.07 (0.068,0.120)</td>
<td>0.03 (0.423,0.529)</td>
<td>-0.24 (&lt;0.0001, &lt;0.0005)*</td>
<td>-0.18 (&lt;0.0001, &lt;0.0005)*</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.15 (&lt;0.0001, &lt;0.0005)*</td>
<td>0.09 (0.011, 0.028)*</td>
<td>-0.01 (0.887, 0.88)</td>
<td>0.19 (&lt;0.0001, &lt;0.0005)*</td>
<td>0.17 (&lt;0.0001, &lt;0.0005)*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BP Measures</th>
<th>Systolic Velocity (Wave 2)</th>
<th>Mean Velocity (Wave 2)</th>
<th>Diastolic Velocity (Wave 2)</th>
<th>Pulsatility Index (Wave 2)</th>
<th>Resistivity Index (Wave 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>0.02 (0.536, 0.596)</td>
<td>-0.01 (0.757, 0.850)</td>
<td>-0.06 (0.114, 0.147)</td>
<td>0.11 (0.004, 0.014)*</td>
<td>0.10 (0.013, 0.022)*</td>
</tr>
<tr>
<td>Mean BP</td>
<td>-0.10 (0.009, 0.018)*</td>
<td>-0.10 (0.008, 0.018)*</td>
<td>-0.08 (0.029, 0.031)*</td>
<td>-0.04 (0.349, 0.400)</td>
<td>-0.01 (0.722, 0.75)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-0.20 (&lt;0.0001,&lt;0.0005)*</td>
<td>-0.17 (&lt;0.0001, &lt;0.0005)*</td>
<td>-0.09 (0.024, 0.029)*</td>
<td>-0.18 (&lt;0.0001, &lt;0.005)*</td>
<td>-0.12 (0.002, 0.003)*</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.13 (&lt;0.0001, &lt;0.0004)*</td>
<td>0.11 (0.004, 0.010)*</td>
<td>0.05 (0.217, 0.271)</td>
<td>0.12 (0.002, 0.007)*</td>
<td>0.10 (0.012, 0.022)*</td>
</tr>
</tbody>
</table>

Values are standardized $\beta$ (P-value, false-discovery rate corrected P-values) for the sitting BP measures predicting ICA blood velocity measures after accounting for covariates. See Table S3 for full covariate effects. BP indicates blood pressure; and ICA, internal carotid artery.

*Associations that remained significant after applying a correction for false-discovery rate.
scores. At wave 1, higher mean BP (β = 0.09; P = 0.02; Figure; Tables 3 and 4; Figure S1) and DBP (β = 0.08; P = 0.04) were weakly associated with larger WMH volume, with similar but weaker associations at wave 2. Higher Fazekas scores (Table S4) were significantly associated with higher SBP (wave 1: β = 0.12; P = 0.002), mean BP (wave 1: β = 0.13; P = 0.001) and DBP (wave 1: β = 0.11; P = 0.003), with similar but weaker associations at wave 2. No association was found between WMH measures (WMH volume or Fazekas) and pulse pressure or variability (Table S2). All the significant associations remained significant after correction for false-discovery rate.

**ICA Blood Velocity Measures and WMH Measures**

Without accounting for BP measures (Figure; Tables 3 and 4), larger WMH volume was associated with higher ICA pulsatility index (β = 0.09; P = 0.016), and higher Fazekas scores (Table S4) were associated with lower ICA diastolic velocity (β = −0.11; P = 0.005) and higher resistivity index (β = 0.08; P = 0.04) but no other ICA blood velocity measures. Accounting for BP measures (Figure; Tables S5 and S7) resulted in marginal adjustments to these associations, larger WMH volume (β = 0.13; P = 0.002) and higher Fazekas scores (β = 0.12; P = 0.003) were associated with higher ICA pulsatility index; higher Fazekas scores were also associated with lower ICA diastolic velocity (β = −0.11; P = 0.005) and higher resistivity index (β = 0.11; P = 0.005). The associations between ICA pulsatility and resistivity indices and WMH remained after false-discovery rate correction. No association was found between WMH and other ICA blood velocity measures, but those with history of hypertension had larger WMH volumes (Tables 3 and 4; β = 0.13; P < 0.001) and higher Fazekas scores (Table S4; β = 0.16; P < 0.001).

**Sensitivity Analyses**

The associations among BP, ICA parameters, and WMH were slightly stronger in hypertensive subjects than in normotensive subjects, but there were no differences in direction of association or other features (Table S6). After converting standardized to unstandardized β, for every 1-year increase in age there was approximately a 2.43 cm³ increase in WMH volume. In addition, for every additional individual diagnosis of hypertension, there was ≈3.47 cm³ increase in WMH volume.

**Discussion**

We investigated associations between BP parameters measured longitudinally, ICA velocity parameters, and WMH in ≈700 community-dwelling individuals aged ≈73 years. Higher SBP, mean BP, and DBP were weakly associated with WMH, especially for BP measured several years previously. Considering the route by which BP effects reach the brain, higher concurrent ICA pulsatility index, largely the result of falling DBP, was associated with WMH (Figure). All associations remained significant after correcting for multiple testing and whether hypertension was included in the model. Thus, the association between BP measures and WMH is different from that between BP measures and WMH when the route between the heart and the brain via the ICAs is accounted for meaning that BP and WMH either associate indirectly through BP elevation earlier in life leading to stiffer vessels which in turn lead to WMH or hypertension and WMH associate through advancing age and stiffer vessels. In either case, the data suggest that the route from BP to WMH is indirect in community-dwelling, generally healthy older subjects. Notably, even within this narrow age-range, as little as a 1-year increase in age was associated with 2.43-mL increase in WMH volume, and hypertension (versus no hypertension) was associated with 3.47-mL increase in WMH volume. This novel finding provides important quantitative information on the effect of age and hypertension on WMH.

**Comparison With Literature**

Our large sample of subjects (694) with longitudinal BP assessments fell within a narrow age-range in their late 60s to early 70s at the 2 waves and were living in the community. The proportion with cardiovascular conditions and risk factors increased for the 3 years, with hypertension increasing from 38% to 50% consistent with previous studies.8–10,24–28 The proportion with cardiovascular conditions and risk factors increased for the 3 years, with hypertension increasing from 38% to 50% consistent with previous studies.8–10,24–28

### Table 3. Association Between White Matter Hyperintensities Volume and Measures of BP (Standardized β [P Value, False-Discovery Rate Corrected P Values])

<table>
<thead>
<tr>
<th>Measures of BP at Waves 1 or 2</th>
<th>BP Measures</th>
<th>ICV</th>
<th>Sex</th>
<th>Age, d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, wave 1</td>
<td>0.08* (0.043,* 0.057)</td>
<td>0.12* (0.021)*</td>
<td>0.08 (0.126)</td>
<td>0.15 (&lt;0.0001)</td>
</tr>
<tr>
<td>Systolic BP, wave 2</td>
<td>0.06 (0.113, 0.248)</td>
<td>0.12 (0.019)</td>
<td>0.08 (0.123)</td>
<td>0.14 (&lt;0.0001)</td>
</tr>
<tr>
<td>Mean BP, wave 1</td>
<td>0.09* (0.021,* 0.057)</td>
<td>0.11* (0.023)*</td>
<td>0.08 (0.118)</td>
<td>0.15* (&lt;0.0001)*</td>
</tr>
<tr>
<td>Mean BP, wave 2</td>
<td>0.06 (0.144, 0.248)</td>
<td>0.12 (0.02)</td>
<td>0.08 (0.131)</td>
<td>0.14 (&lt;0.0001)</td>
</tr>
<tr>
<td>Diastolic BP, wave 1</td>
<td>0.08* (0.036,* 0.057)</td>
<td>0.11* (0.025)*</td>
<td>0.08 (0.121)</td>
<td>0.15* (&lt;0.0001)*</td>
</tr>
<tr>
<td>Diastolic BP, wave 2</td>
<td>0.04 (0.306, 0.306)</td>
<td>0.12 (0.021)</td>
<td>0.08 (0.123)</td>
<td>0.14 (&lt;0.0001)</td>
</tr>
<tr>
<td>Pulse pressure, wave 1</td>
<td>0.04 (0.249, 0.249)</td>
<td>0.12 (0.02)</td>
<td>0.07 (0.142)</td>
<td>0.14 (&lt;0.0001)</td>
</tr>
<tr>
<td>Pulse pressure, wave 2</td>
<td>0.05 (0.186, 0.248)</td>
<td>0.12 (0.021)</td>
<td>0.08 (0.131)</td>
<td>0.14 (&lt;0.0001)</td>
</tr>
</tbody>
</table>

Models accounted for all covariates. Dependent variables were measures of white matter hyperintensities, whereas independent variables were measures of internal carotid artery velocities and of BP. Each row represents a separate model which controlled for ICV and demographic variables. Health variables’ inclusion used stepwise method and only those that passed the Akaike Information Criterion test appeared in the final model above. BP indicates blood pressure; and ICV, intracranial volume.

*Indicates associations that were significant.
Table 4. Association Between White Matter Hyperintensities Volume and Measures of ICA Blood Velocity (Standardized β [P Value, False-Discovery Rate Corrected P Values])

<table>
<thead>
<tr>
<th>Measure of ICA Velocity at Wave 2</th>
<th>ICA Velocity Measures</th>
<th>Covariates</th>
<th>ICV</th>
<th>Sex</th>
<th>Age, d</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic velocity</td>
<td>0.04 (0.343, 0.428)</td>
<td>0.13 (0.011)</td>
<td>0.14 (&lt;0.0001)</td>
<td>0.13 (&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean velocity</td>
<td>0.00 (0.990, 0.990)</td>
<td>0.13 (0.011)</td>
<td>0.13 (&lt;0.0001)</td>
<td>0.13 (&lt;0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic velocity</td>
<td>−0.05 (0.178, 0.283)</td>
<td>0.13 (0.012)</td>
<td>0.13 (0.001)</td>
<td>0.13 (0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulsatility index</td>
<td>0.09* (0.016, *0.08)</td>
<td>0.12 (0.014)</td>
<td>0.13 (&lt;0.0001)</td>
<td>0.12 (0.002)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistivity index</td>
<td>0.07 (0.054, 0.135)</td>
<td>0.12 (0.015)</td>
<td>0.14 (&lt;0.0001)</td>
<td>0.13 (0.001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Models accounted for all covariates. Dependent variables were measures of white matter hyperintensities, whereas independent variables were measures of ICA velocities and of blood pressure. Each row represents a separate model which controlled for ICV and demographic variables. Health variables’ inclusion used stepwise method and only those that passed the Akaike Information Criterion test appeared in the final model above. ICA indicates internal carotid artery; and ICV, intracranial volume.

*Indicates associations that were significant.

association among higher SBP, mean BP, DBP, and WMH is consistent with many previous studies.3,5,8,29-32

Some studies9,10 have reported associations between WMH and ICA or MCA pulsatility index, but no previous studies examined associations among BP, ICA parameters, and WMH simultaneously or longitudinally or the role of falling DBP identified in this study. Increased arterial stiffness (measured in various ways, in various arteries) and WMH are emerging: 167 patients with hypertension,12 363 community-dwelling subjects,1 in hypertensive subjects among 1460 community-dwelling subjects,3 in 1587 Framingham subjects,13 in 1800 subjects in the 3C-Dijon Study,34 and in 1270 Dallas Heart Study,35 but none of these studies dissected the complete path from BP via carotid to brain and the subjects’ ages covered several decades. One study of 303 elderly subjects found that pulse wave velocity predicted WMH assessed 10 years later but in only 1 white matter tract (the superior longitudinal fasciculus).36 Lower aortic DBP, increased aortic pulse pressure, and increased MCA pulsatility index were associated with WMH in 100 patients with stroke of wide age-range,10 similar to our findings and suggesting a coassociation rather than a direct association. The powerful effects of age on many biological processes are difficult to correct statistically: in addition to our 2.43-mL/y increase in WMH, MCA flow velocity falls by 0.2 cm/s per year increase in age (P=0.045) and by 3.75 cm/s per point increase in WMH Fazekas score (P=0.004). Consequently, MCA pulsatility index has even been suggested as an office screening tool for WMH.37

We did not find associations of WMH with BP variability although our data were limited for assessing variability, but this is consistent with 2 other large recent prospective studies,31,32 which disagreed with previous cross sectional studies showing BP variability-WMH associations.38,39

BP, ICA Velocities, and Potential Pathophysiological Effects on WMH

In our study, SBP did not change between waves 1 and 2, but DBP fell and consequently pulse pressure increased. Lower DBP, higher pulse pressure and higher ICA pulsatility index, mean and diastolic velocity were consistently associated, but SBP associations were generally inconsistent and weak. After adjusting for BP, larger WMH volume was associated with higher ICA pulsatility index and lower DBP. The pathway from BP to WMH is, therefore, through falling DBP, rising pulse pressure, and ICA pulsatility index. Increased vessel stiffness would fit with emerging evidence that WMH associate more with BP levels taken years earlier than with concurrent readings. Associations between BP and WMH when ICA parameters are not considered, in which SBP is most prominent, are contrary to the direct path of BP transmission to the brain via the carotid arteries where lower DBP is the associated variable. This might suggest that DBP was falling below an acceptable perfusion pressure to result in WMH, but the DBP values (mean, 78.1; SD, 9.68; Table 1) do not suggest that is likely.

Strengths

Strengths include using well-validated image processing tools, accounting for all necessary covariates in the statistical models, and comprehensive assessment of several BP measures at sitting and standing positions, at ages 70 and 73 years; 5 ICA blood velocity measures averaged across right and left and 2 measures of WMH recorded at mean age 73 years. ICA and MCA pulsatility index are closely related; brachial pulse pressure (as measured here) showed the strongest correlation with MCA pulsatility index and explained the largest variance in MCA pulsatility index.5

Limitations

We cannot comment on longitudinal WMH or ICA velocity parameters. The LBC193615,16 participants are currently undergoing repeat MRI to provide longitudinal data. Our variability measures were limited, but other studies with comprehensive longitudinal visit-to-visit variability measures have not found associations.32,40 We did not account for medical treatment, but the risk factor diagnoses and BP measures encompass treatment. Others have shown that BP levels are more important than treatment per se in relation to WMH.35 We calculated mean velocity to avoid errors in machine-calculated values that may have under- or overestimated the time averaged mean; however, pulsatility index (the strongest covariate) is the same whether calculated by hand or machine.

Perspectives

That the association between BP and WMH may be a coassociation acting through increased arterial stiffness has implications for strategies to prevent WMH progression and their
cognitive and physical consequences. Treatment of hypertension is important for stroke prevention, but there is less evidence that it reduces WMH progression\(^1\)\(^2\) (but BP lowering may have been too little or not for long enough) and mixed information about effects on cognition (results of the Secondary Prevention of Small Subcortical Stroke [SPS3] trial on BP lowering in ≥3000 patients with lacunar stroke are awaited). Perhaps therapies to reduce arterial/arteriolar stiffness, by acting more directly on the suggested pathophysiological pathway to WMH, might have valuable effects on preventing WMH progression. Our data suggest that lifestyle or pharmacological methods to reduce arterial stiffness preferentially would be worth evaluating in case some antihypertensive therapies alone are insufficient to restore normal vascular tone and cerebral vasoreactivity.

**Conclusions**

The association between BP and WMH at older ages, when considering the path via the carotid arteries, is most closely aligned with increased ICA pulsatility index, which was a consequence of falling DBP, questioning the directness of the link between BP and WMH. Longitudinal studies with narrow age-range subjects help to differentiate potentially causal relationships from shared, age-related coassociations. Determining whether it is falling or rising BP in later life that increases risk of WMH, and differential age effects, is important for future prevention of the stroke and dementia consequences of small vessel disease.

**Acknowledgments**

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**Disclosures**

None.

**References**


Blood Pressure, Internal Carotid Artery Flow Parameters, and Age-Related White Matter Hyperintensities

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BLOOD PRESSURE, INTERNAL CAROTID ARTERY FLOW PARAMETERS AND AGE-RELATED WHITE MATTER HYPERINTENSITIES - Online-Only Supplementary Material

Benjamin S Aribisala$^{1,2,3,4}$, Zoe Morris$^{1,5}$, Elizabeth Eadie, $^{1,5}$ Avril Thomas, $^{1,5}$ Alan Gow$^{6,8}$, Maria C Valdés Hernández$^{1,2,3}$, Nataile A Royle$^{1,2,3}$, Mark E Bastin$^{1,2,3}$ John Starr$^{2,7}$, Ian J Deary$^{6,8}$, Joanna M Wardlaw$^{1,2,3}$

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$^4$Computer Science Department, Lagos State University, Nigeria
$^5$Department of Neuroradiology, Western General Hospital, NHS Lothian
$^6$Department of Psychology, University of Edinburgh, Edinburgh, UK
$^7$Geriatric Medicine Unit, University of Edinburgh, Edinburgh, UK
$^8$Psychology, School of Life Sciences, Heriot-Watt University, Edinburgh, UK
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- **Supplementary Table S2** Association between measures of WMH (WMH volume and Fazekas scores) and variability BP. Models accounted for all covariates

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- **Fazekas scores – Supplementary Table S5** Association between measures of blood velocity in the ICA and WMH Fazekas scores after correcting for measures of BP

- **Text on hypertension/ no hypertension**

- **Supplementary Table S6** Associations between BP, ICA and WMH. Analysis grouped using history of hypertension. Values are $r$ ($p$)

- **Supplementary Table S7** Association between ICA blood velocity parameters and WMH volume after correcting for measures of BP, (standardized $\beta$ ($p$ value, FDR corrected $p$values).

- **Figure S1** Scatter plots of the bivariate associations between BP, ICA blood velocity parameters and WMH

- **References**
Association between BP variability, ICA and WMH

Variability in BP has recently been suggested as a marker of hypertension and a risk factor for stroke.\textsuperscript{1,2} None of the existing studies of the association between BP, internal carotid artery or middle carotid artery velocity parameters and WMH investigated BP variability. Here we investigated the association between BP variability measured longitudinally, ICA blood flow velocity parameters and age-related WMH.

Variability was calculated using five different methods proposed previously:\textsuperscript{3-5} standard deviation (SD), coefficient of variation (standard deviation of successive measurements divided by their mean value), average real variability (average absolute difference between successive measurements) and successive variation (average squared difference between successive measurements). Variability was computed separately for systolic and diastolic BP, and for each time point using the three sitting (or standing) BP measurements.

Variability BP at time point 1 and 2 were compared using paired t-tests and associations between variability BP, ICA blood flow parameters and WMH were investigated using multivariate linear regression models. The covariates which are known or proposed predictors of WMH, BP or blood velocity parameters were included in the analysis: were age in days at MRI, sex, body mass index (BMI), and self-reported history of ischemic heart disease, stroke, peripheral vascular diseases (PVD), other circulatory disorder, diabetes, hypertension, smoking (ever smoked previously or currently), and hypercholesterolemia.

All measures of BP variability investigated (standard deviation, coefficient of variation, average real variability and successive variation) gave similar results; therefore, for brevity, only the results of coefficient of variation (hereafter referred to as variability BP) are presented. BP variability (systolic: 4.09 ± 2.36 to 3.84 ± 2.31, diastolic: 4.27 ± 2.97 to 3.77 ± 2.56) all reduced significantly (p<0.001) from time point 1 to 2.

There was no significant association between variability BP and almost all measures of ICA blood flow parameters (Supplementary Table 2) or measures of WMH (Supplementary Table 3). In conclusion, we did not find any significant association between WMH and any of four different measures of BP variability (standard deviation, coefficient of variation, average real variability, and successive variation), consistent with another similar study that did not find any association between WMH and BP variability.\textsuperscript{6} However, we computed variability BP
using three BP readings, which could be too few to give reliable measures of variability, hence limiting generalisation of results. More data are required to determine the role of BP variability in WMH and stroke risk.
Supplementary Table S1. Association between variability BP and measures of blood velocity in the ICA

| BP Measures | Systolic velocity Mean velocity | Diastolic velocity Pulsatility index Resistivity index |
|-------------|--------------------------------|---------------------------------|-----------------|----------------|----------------|
| Wave 1      |                                |                                 |                 |                |                |
| Systolic BP variability | 0.00 (0.957) | -0.01 (0.79) | -0.03 (0.501) | 0.04 (0.319) | 0.05 (0.18) |
| Diastolic BP variability | 0.01 (0.777) | 0.01 (0.852) | 0.00 (0.987) | 0.03 (0.497) | 0.03 (0.377) |
| Wave 2      |                                |                                 |                 |                |                |
| Systolic BP variability | 0.05 (0.163) | 0.04 (0.316) | 0.01 (0.79) | 0.05 (0.158) | 0.06 (0.148) |
| Diastolic BP variability | 0.04 (0.331) | 0.01 (0.717) | -0.02 (0.569) | **0.08 (0.036)** | **0.08 (0.039)** |

Note. Values are the standardized $\beta$ (and $p$ value) for the listed variability BP predicting measures of blood velocity in the internal carotid arteries after accounting for all the covariates in the model. The covariates included were sex, age, BMI, history of: stroke, smoking, ischemic heart disease, diabetes, hypercholesterolemia, History of peripheral vascular diseases and blood circulation problem. BP variability represents the coefficient of variations (standard deviation of successive measurements divided by their mean value). BP measures were recorded at sitting position. Standing BP measures (not presented for brevity) were similar to those of sitting BP.

Model: $BP = \beta_1*ICA + \beta_2*Sex + \beta_3*age + \beta_4*BMI + \beta_5*stroke + \beta_6*smoking + \beta_7*$ ischemic heart disease + $\beta_8$*hypercholesterolemia + $\beta_9$*peripheral vascular disease + $\beta_{10}$*blood circulation problem

Where BP represents variability BP and ICA represents measures of ICA velocity
### Supplementary Table S2. Association between measures of WMH (WMH volume and Fazekas scores) and variability BP. Models accounted for all covariates

<table>
<thead>
<tr>
<th>Measures of BP</th>
<th>BP Measures</th>
<th>Covariates</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>WMH volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>variability, wave 1</td>
<td>0.00(0.97)</td>
<td>0.12 (0.021)</td>
<td>0.08 (0.138)</td>
</tr>
<tr>
<td>variability, wave 2</td>
<td>0.00(0.998)</td>
<td>0.12 (0.021)</td>
<td>0.08 (0.138)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>variability, wave 1</td>
<td>0.00(0.977)</td>
<td>0.12 (0.021)</td>
<td>0.08 (0.138)</td>
</tr>
<tr>
<td>variability, wave 2</td>
<td>-0.03 (0.428)</td>
<td>0.11 (0.025)</td>
<td>0.07 (0.15)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measures of BP</th>
<th>BP Measures</th>
<th>Covariates</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fazekas Scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>variability, wave 1</td>
<td>-0.04 (0.284)</td>
<td>0.07 (0.088)</td>
<td>0.05 (0.237)</td>
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<td>variability, wave 2</td>
<td>0.02 (0.616)</td>
<td>0.07 (0.089)</td>
<td>0.05 (0.214)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>variability, wave 1</td>
<td>0.02 (0.532)</td>
<td>0.06 (0.104)</td>
<td>0.05 (0.203)</td>
</tr>
<tr>
<td>variability, wave 2</td>
<td>0.00(0.928)</td>
<td>0.06 (0.096)</td>
<td>0.05 (0.217)</td>
</tr>
</tbody>
</table>

**Note:** Dependent variables were measures of WMH while independent variables were variability BP. Each row represents a separate model which controlled for ICV and demographic variables. Health variables’ inclusion used stepwise method and only those that passed the Akaike Information Criterion test appeared in the final model above. Values are standardized β (and p value). Significant values are in boldface. BP variability represents the coefficient of variations (standard deviation of successive measurements divided by their mean value). BP measures were recorded at sitting position. Standing BP results (not presented for brevity) were similar to those of sitting BP.
Model: WMH = β1*BP + β2*Sex + β3*age + β4*BMI + β5*stroke + β6*smoking +
β7*hypertension + β8* ischemic heart disease + β9*hypercholesterolemia + β10*peripheral
vascular disease + β11*blood circulation problem

Where WMH represents measures of white matter hyperintensities (volume or Fazekas
scores) and BP represents variability BP.
**Supplementary Table S3.** Details of covariate effects and measures of blood velocity in the ICA. Models accounted for all covariates

<table>
<thead>
<tr>
<th>Parameter assessed</th>
<th>Wave 1 -BP</th>
<th>Wave 2 -BP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Systolic velocity</td>
<td>Mean velocity</td>
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<tr>
<td>Systolic BP</td>
<td>0.06</td>
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<tr>
<td>Sex</td>
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<td>0.08</td>
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<tr>
<td>Age in days</td>
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<td>BMI</td>
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<tr>
<td>History of cardiovascular disease</td>
<td>0.07</td>
<td>0.05</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>History of stroke</td>
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</tr>
<tr>
<td>History of smoking</td>
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<td>0.18</td>
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<td>0.04</td>
</tr>
<tr>
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<tr>
<td>Problems with blood circulation</td>
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<td>-0.06</td>
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<tr>
<td>History of stroke</td>
<td>0.16†</td>
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Note: † indicates significant positive correlation, * indicates significant negative correlation.
<table>
<thead>
<tr>
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<th>Leg pain when walking or in bed at night</th>
<th>Problems with blood circulation</th>
<th>BMI</th>
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<th>History of diabetes</th>
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<tr>
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<td>-0.0</td>
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<td>0.04</td>
<td>0.02</td>
<td>-0.0</td>
<td>-0.0</td>
<td>-0.0</td>
<td>-0.0</td>
<td>-0.0</td>
<td>-0.0</td>
<td>-0.0</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Note: Values are the standardized β for the BP variables and covariates. Dependent variables were measures of blood velocity (measured only at the second time point) while independent variables were measures of BP (measured at time points 1 and 2). Models corrected for all covariates.
Supplementary Table S4. Association between WMH Fazekas scores and measures of BP and ICA blood velocity (standardized $\beta$ ($p$ value)). Models accounted for all covariates

<table>
<thead>
<tr>
<th>Measures of BP</th>
<th>BP Measures</th>
<th>Sex</th>
<th>Age in days</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, wave 1</td>
<td>0.12 (0.002)*</td>
<td>0.07 (0.063)</td>
<td>0.05 (0.165)</td>
<td>0.09 (0.016)</td>
</tr>
<tr>
<td>Systolic BP, wave 2</td>
<td>0.09 (0.026)*</td>
<td>0.07 (0.082)</td>
<td>0.04 (0.258)</td>
<td>0.10 (0.009)</td>
</tr>
<tr>
<td>Mean BP, wave 1</td>
<td>0.13 (0.001)*</td>
<td>0.07 (0.052)</td>
<td>0.06 (0.131)</td>
<td>0.09 (0.014)</td>
</tr>
<tr>
<td>Mean BP, wave 2</td>
<td>0.1 (0.012)*</td>
<td>0.07 (0.07)</td>
<td>0.04 (0.253)</td>
<td>0.10 (0.007)</td>
</tr>
<tr>
<td>Diastolic BP, wave 1</td>
<td>0.11 (0.003)*</td>
<td>0.07 (0.054)</td>
<td>0.06 (0.126)</td>
<td>0.10 (0.012)</td>
</tr>
<tr>
<td>Diastolic BP, wave 2</td>
<td>0.08 (0.03)*</td>
<td>0.07 (0.069)</td>
<td>0.05 (0.232)</td>
<td>0.10 (0.007)</td>
</tr>
<tr>
<td>Pulse pressure, wave 1</td>
<td>0.07 (0.054)</td>
<td>0.07 (0.087)</td>
<td>0.05 (0.211)</td>
<td>0.09 (0.014)</td>
</tr>
<tr>
<td>Pulse pressure, wave 2</td>
<td>0.07 (0.069)</td>
<td>0.07 (0.087)</td>
<td>0.05 (0.189)</td>
<td>0.09 (0.02)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measure of ICA velocity measures</th>
<th>ICA velocity measures</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic velocity</td>
<td>-0.04 (0.362)</td>
<td>Sex</td>
</tr>
<tr>
<td>Mean velocity</td>
<td>-0.06 (0.091)</td>
<td>Doppler</td>
</tr>
<tr>
<td>Diastolic velocity</td>
<td>-0.1 (0.012)*</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td>0.08 (0.051)</td>
<td></td>
</tr>
<tr>
<td>Resistivity index</td>
<td>0.08 (0.038)</td>
<td></td>
</tr>
</tbody>
</table>
### Predicting WMH Fazekas Scores from measures of ICA Flow Velocities

<table>
<thead>
<tr>
<th>Measures of ICA flow velocities</th>
<th>ICA velocity measures</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sex</td>
</tr>
<tr>
<td>Mean systolic velocity</td>
<td>-0.04</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>(0.314)</td>
<td>(0.066)</td>
</tr>
<tr>
<td>Mean velocity</td>
<td>-0.06</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>(0.09)</td>
<td>(0.06)</td>
</tr>
<tr>
<td>Mean diastolic velocity</td>
<td>-0.10</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>(0.021)</td>
<td>(0.043)</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td>0.05</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>(0.18)</td>
<td>(0.03)</td>
</tr>
<tr>
<td>Resistivity index</td>
<td>0.08</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>(0.04)</td>
<td>(0.05)</td>
</tr>
</tbody>
</table>

* represent associations that remained significant after applying a correction for false discovery rate

See note Table 3 for modelling approach
### Supplementary Table S5. Association between measures of blood velocity in the ICA and WMH Fazekas scores after correcting for measures of BP

<table>
<thead>
<tr>
<th>Measures of ICA velocity</th>
<th>ICA velocity measures</th>
<th>Covariates</th>
<th>diastolic BP, wave 1</th>
<th>diastolic BP, wave 2</th>
<th>Systolic BP, wave 1</th>
<th>Systolic BP, wave 2</th>
<th>History of stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex</td>
<td>Age in days</td>
<td>Sex</td>
<td>Age in days</td>
<td>Sex</td>
<td>Age in days</td>
<td>Sex</td>
</tr>
<tr>
<td>Systolic velocity</td>
<td>-0.03 (0.517)</td>
<td>0.07 (0.056)</td>
<td>0.05 (0.206)</td>
<td>0.03 (0.644)</td>
<td>0.03 (0.627)</td>
<td>0.07 (0.237)</td>
<td>0.03 (0.641)</td>
</tr>
<tr>
<td>Mean velocity</td>
<td>-0.07 (0.097)</td>
<td>0.08 (0.05)</td>
<td>0.05 (0.24)</td>
<td>0.03 (0.629)</td>
<td>0.02 (0.736)</td>
<td>0.07 (0.23)</td>
<td>0.03 (0.613)</td>
</tr>
<tr>
<td>Diastolic velocity</td>
<td>-0.11 (0.005)*</td>
<td>0.08 (0.03)</td>
<td>0.04 (0.281)</td>
<td>0.04 (0.478)</td>
<td>0.02 (0.764)</td>
<td>0.07 (0.277)</td>
<td>0.02 (0.663)</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td>0.12 (0.003)*</td>
<td>0.1 (0.011)</td>
<td>0.06 (0.139)</td>
<td>0.06 (0.324)</td>
<td>0.06 (0.285)</td>
<td>0.06 (0.323)</td>
<td>-0.02 (0.754)</td>
</tr>
<tr>
<td>Resistivity index</td>
<td>0.11 (0.005)*</td>
<td>0.09 (0.02)</td>
<td>0.06 (0.12)</td>
<td>0.05 (0.388)</td>
<td>0.05 (0.373)</td>
<td>0.06 (0.303)</td>
<td>-0.01 (0.865)</td>
</tr>
</tbody>
</table>

* represent associations that remained significant after applying a correction for false discovery rate

See note Table 3 for modelling approach
Sensitivity analysis: Associations between BP, ICA Flow Parameters and WMH in subjects with versus without hypertension

The aim of this analysis was to determine if there is any difference in associations between BP, ICA blood velocity parameters and WMH for those with or without hypertension. The entire data was grouped into two, those with hypertension and those without. The associations between BP, ICA blood velocity parameters (peak systolic velocity, mean velocity, end diastolic velocity, pulsatility index and resistivity index) and WMH (volume and Fazekas) was investigated using Pearson bivariate analysis. None of the models included any of the covariates, so the results may not be the same with those of the regression analysis reported in the manuscript.

Of the 694 subjects who had completed brain MRI data, 37.10% of the participants had hypertension at the first time point but this increased significantly to 48.70% of the population at the second time point. For the those with history of hypertension, higher ICA systolic velocity was associated with lower mean BP (Supplementary Table 1, time point 1 and 2), lower diastolic BP (time point 1 and 2) and higher pulse pressure (time point 1 and 2). Associations were similar for subjects without hypertension but the association between mean BP and systolic velocity was not significant. Higher ICA mean velocity was associated with lower diastolic BP (time point 1 and 2), lower mean BP (time point 2 only) and higher pulse pressure (time point 1 and 2) in patients with hypertension. In subjects without hypertension, higher ICA velocity was associated with lower diastolic BP (only at time point 2) but not with mean BP or pulse pressure. Higher pulsatility index was associated with lower diastolic BP (time point 1 and 2), lower mean BP (time point 1 and 2) and higher pulse pressure (time point 1 only) in patients with hypertension. Associations were similar for subjects without hypertension, but the associations between pulsatility index and mean velocity were not significant. Higher resistivity index was associated with lower diastolic BP (time point 1 and 2) and higher pulse pressure (time point 1 and 2) in subjects without hypertension but showed a non-significant trend in those with hypertension. No significant association was found between BP and WMH in any of the two groups (with or without hypertension), at time point 1 or 2. Finally, no significant association was found between ICA and WMH volume in any of the two groups. However, higher diastolic velocity was very weakly associated with lower Fazekas scores in those without hypertension but not those with hypertension.
In conclusion, the associations between BP, ICA parameters and WMH were slightly stronger but there were no differences in direction of association or other feature in subjects with versus without hypertension.
**Supplementary Table S6.** Associations between BP, ICA and WMH. Analysis grouped using history of hypertension. Values are r (p)

<table>
<thead>
<tr>
<th>Parameter assessed</th>
<th>Time point 1: BP and ICA</th>
<th>Time point 2: BP and ICA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypertension  = 37.10%</td>
<td>Without Hypertension = 62.90%</td>
</tr>
<tr>
<td>BP</td>
<td>Systolic ICA</td>
<td>mean velocity</td>
</tr>
<tr>
<td>Mean BP</td>
<td>-0.126 (0.044)</td>
<td>-0.06 (0.34)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>-0.232 (&lt;0.001)</td>
<td>-0.139 (0.026)</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.181 (0.004)</td>
<td>0.143 (0.022)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>BP</th>
<th>WMH Fazekas</th>
<th>BP WMH Fazekas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>-0.051 (0.425)</td>
<td>0.039 (0.536)</td>
</tr>
<tr>
<td>Mean BP</td>
<td>-0.057 (0.365)</td>
<td>0.031 (0.62)</td>
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<tr>
<td>Diastolic BP</td>
<td>-0.049 (0.437)</td>
<td>0.016 (0.793)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter assessed</th>
<th>Time point 1: BP and WMH</th>
<th>Time point 2: BP and WMH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypertension = 48.70%</td>
<td>Without Hypertension = 51.30%</td>
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<tr>
<td>BP</td>
<td>Systolic ICA</td>
<td>mean velocity</td>
</tr>
<tr>
<td>Mean BP</td>
<td>-0.276 (&lt;0.001)</td>
<td>-0.278 (&lt;0.001)</td>
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<tr>
<td>Diastolic BP</td>
<td>-0.345 (&lt;0.001)</td>
<td>-0.321 (&lt;0.001)</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.207 (0.001)</td>
<td>0.213 (0.001)</td>
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</table>

<table>
<thead>
<tr>
<th>BP</th>
<th>Systolic ICA</th>
<th>mean velocity</th>
<th>pulsatility index</th>
<th>Resistivity index</th>
<th>Wave 2</th>
<th>Systolic ICA</th>
<th>mean velocity</th>
<th>pulsatility index</th>
<th>Resistivity index</th>
</tr>
</thead>
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<tr>
<td>Systolic BP</td>
<td>0.045 (0.482)</td>
<td>0.076 (0.226)</td>
<td>0.068 (0.281)</td>
<td>-0.055 (0.381)</td>
<td>Systolic BP</td>
<td>0.067 (0.167)</td>
<td>0.066 (0.173)</td>
<td>0.067 (0.172)</td>
<td>0.086 (0.076)</td>
</tr>
<tr>
<td>Mean BP</td>
<td>0.037 (0.557)</td>
<td>0.059 (0.346)</td>
<td>0.068 (0.281)</td>
<td>-0.055 (0.381)</td>
<td>Mean BP</td>
<td>0.067 (0.172)</td>
<td>0.086 (0.076)</td>
<td>0.051 (0.298)</td>
<td>0.086 (0.074)</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.021 (0.737)</td>
<td>0.029 (0.646)</td>
<td>0.068 (0.281)</td>
<td>-0.055 (0.381)</td>
<td>Diastolic BP</td>
<td>0.067 (0.172)</td>
<td>0.086 (0.076)</td>
<td>0.051 (0.298)</td>
<td>0.086 (0.074)</td>
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</table>

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<th>ICA and WMH</th>
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</thead>
<tbody>
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<td>WMH Fazekas</td>
</tr>
<tr>
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<td>-0.1 (0.118)</td>
</tr>
<tr>
<td>Diastolic ICA</td>
<td>-0.046 (0.353)</td>
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<tr>
<td>Pulsatility index</td>
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<tr>
<td>Pulsatility index</td>
<td>0.079 (0.107)</td>
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**Supplementary Table S7:** Association between ICA blood velocity parameters and WMH volume after correcting for measures of BP, (standardized β value, FDR corrected p values).

Predicting WMH from measures of ICA velocity

<table>
<thead>
<tr>
<th>Measures of ICA velocity</th>
<th>ICA velocity</th>
<th>ICV</th>
<th>Sex</th>
<th>Age in days</th>
<th>diastolic BP, wave 1</th>
<th>diastolic BP, wave 2</th>
<th>systolic BP, wave 1</th>
<th>systolic BP, wave 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic velocity</td>
<td>0.05 (0.257, 0.321)</td>
<td>0.12 (0.023)</td>
<td>0.08 (0.108)</td>
<td>0.15 (&lt;0.0001)</td>
<td>0.06 (0.306)</td>
<td>-0.01 (0.856)</td>
<td>0.01 (0.873)</td>
<td>0.05 (0.415)</td>
</tr>
<tr>
<td>Mean velocity</td>
<td>0.00 (0.981, 0.981)</td>
<td>0.12 (0.023)</td>
<td>0.08 (0.113)</td>
<td>0.14 (&lt;0.0001)</td>
<td>0.06 (0.345)</td>
<td>-0.02 (0.688)</td>
<td>0.02 (0.804)</td>
<td>0.05 (0.362)</td>
</tr>
<tr>
<td>Diastolic velocity</td>
<td>-0.06 (0.101, 0.168)</td>
<td>0.11 (0.024)</td>
<td>0.08 (0.096)</td>
<td>0.14 (&lt;0.0001)</td>
<td>0.07 (0.283)</td>
<td>-0.04 (0.547)</td>
<td>0.01 (0.829)</td>
<td>0.05 (0.357)</td>
</tr>
<tr>
<td>Pulsatility index</td>
<td><strong>0.13 (0.002, 0.01)</strong>*</td>
<td><strong>0.11 (0.031)</strong></td>
<td>0.10 (0.048)</td>
<td><strong>0.14 (&lt;0.0001)</strong></td>
<td>0.09 (0.145)</td>
<td>0.00 (0.947)</td>
<td>0.00 (0.956)</td>
<td>0.02 (0.72)</td>
</tr>
<tr>
<td>Resistivity index</td>
<td><strong>0.10 (0.014, 0.035)</strong>*</td>
<td><strong>0.11 (0.034)</strong></td>
<td>0.09 (0.082)</td>
<td><strong>0.15 (&lt;0.0001)</strong></td>
<td>0.08 (0.21)</td>
<td>-0.01 (0.877)</td>
<td>0.00 (0.969)</td>
<td>0.03 (0.577)</td>
</tr>
</tbody>
</table>

* represent associations that remained significant after applying a correction for false discovery rate

See note Table 3 for modelling approach
Supplementary Figure 1: Scatter plots of the bivariate associations between BP, ICA blood velocity parameters and WMH (expressed as % of WMH in ICV).

(a) diastolic BP vs WMH, (b) diastolic BP vs ICA diastolic velocity, (c) ICA diastolic velocity vs WMH, (d) pulsatility index vs WMH and (e) pulse pressure vs pulsatility index.
Differences with associations given in the tables are because the tables included multivariate analyses and should be regarded as the primary analyses.
References


