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

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Abstract

White matter hyperintensities (WMH) are associated with hypertension. We examined interactions between 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) 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 age 73 were associated with history of hypertension (β=0.13, $p<0.001$) and with BP at age 70 (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 age 73. Lower diastolic BP and higher pulse pressure were associated with higher ICA pulsatility index at age 73 (diastolic BP: standardized β, age 70=−0.24, $p<0.001$; pulse pressure age 70 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 which leads to WMH over time, or co-associate through advancing age and stiffer vessels, or both. Reducing vascular stiffness may reduce WMH progression and should be tested in randomised trials, in addition to testing antihypertensive therapy.

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Keywords

blood flow velocity; blood pressure; pulse pressure; white matter hyperintensities; ageing; magnetic resonance imaging

Introduction

White matter hyperintensities (WMH) are indicators of cerebral small vessel disease[1] and are implicated in the pathogenesis of cognitive impairment, stroke and dementia.[2] WMH are associated with hypertension and increased risk of stroke,[3-5] 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.[3,6-8] Arterial stiffening impairs the damping of the arterial waveform in large arteries and could lead to excessive transmission of BP pulsation to the brain.[9,10] Increasing stiffness of the large central arteries is associated with WMH.[8-12] 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.[7-9] Since this cyclic variation in BP is transmitted to the brain through the internal carotid arteries (ICA), an association between BP, ICA flow parameters and WMH might be expected.[5] Few studies have compared BP, ICA or middle cerebral artery (MCA) blood flow velocity and WMH.[9,13]

Previous studies[9,10] that investigated BP and/or 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 *and* systolic BP and the relative contribution of these is a function of age: in young adults, both diastolic and systolic BP increase, whereas in the elderly systolic BP increases while diastolic BP reduces with age.[14]

Here we investigated the association between BP measured longitudinally, ICA blood flow velocity parameters and age-related WMH in a well characterised large community-dwelling cohort of older adults with a narrow age range. We hypothesised that as 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 blood pressure and WMH at older ages.

Methods

Subjects

Study participants were members of the Lothian Birth Cohort 1936 (LBC1936).[15] They were all born in 1936, most undertook the Scottish Mental Survey of 1947,[15] and most were living in the Lothian (Edinburgh) area of Scotland when first recruited into the LBC1936 between 2004 and 2007. At mean age 70 years (LBC1936 wave 1), 1091 participants undertook detailed medical and cognitive assessments.[15] 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).[16]

Subjects provided history of ischemic heart disease, diabetes, hypertension (diagnosed or on treatment), smoking (coded here as ever smoked previously or currently),

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hypercholesterolemia, peripheral vascular disease (PVD), 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 wave 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 systolic and diastolic BP were taken, sitting and standing. We calculated average systolic and diastolic BP over the three sittings (or standings) and pulse pressure for each wave. Brachial pulse pressure closely reflects aortic pulse pressure – of five 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.[5] We also calculated mean BP (equation 1, SBP and DBP are the systolic and diastolic BP respectively).

$$\text{Mean } BP = \frac{SBP - DBP}{3} + DPB \quad 1$$

We calculated BP variability using methods proposed previously:[17-19] 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), separately for systolic and diastolic BP (Supplementary Tables S1 and S2), and for each time point using the three sitting (or standing) BP measurements. Note the availability of three 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 Colour Doppler scanner (Siemens AG, Erlangen, Germany) with 7.5 MHz variable frequency probe by experienced neurovascular ultrasonographers. Blood flow velocity readings were obtained, after at least five minutes rest supine with head on pillow, from the left and right common, internal and external carotid arteries,[20] 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 (ICAS=ICA systolic velocity and ICAD=ICA end diastolic velocity). We calculated mean velocity,[20,21] rather than using the machine-derived time averaged mean, to avoid inaccurate machine calculations occurring secondary to signal drop out or artefact from the velocity waveform. ICA velocity parameters including pulsatility and resistivity indices, closely reflect intracranial arterial velocity parameters.[5] Measuring blood velocity parameters in the ICAs avoids the problem of a) the ≥10% data loss due to acoustically dense skull and b) incorrect middle cerebral artery velocity calculations due to assumed angle of insonance that occur with transcranial Doppler ultrasound.

$$\text{Mean velocity} = \frac{ICAS - ICAD}{3} + ICAD \quad 2$$

$$\text{Pulsatility Index} = \frac{ICAS - ICAD}{\text{Mean velocity}} \quad 3$$

$$\text{Resistivity Index} = \frac{ICAS - ICAD}{ICAS} \quad 4$$

Magnetic Resonance Brain Imaging

We report the imaging findings according to the Standards for Reporting Vascular Changes in Neurodegeneration (STRIVE) criteria.[1] All brain MRI data were acquired at wave 2 on a 1.5T GE Signa Horizon HDx scanner (General Electric, Milwaukee, WI, USA) with a self-shielding gradient set, maximum gradient strength 33 mT/m, and an 8-channel phased-array head coil. The image acquisition included: T_1-weighted coronal, T_2-weighted, T_2*-weighted and FLAIR (Fluid Attenuated Inversion Recovery) sagittal whole brain scans (details in[16]). WMH were segmented and volumes measured using a validated multispectral image processing tool, MCMxxxVI (www.sourceforge.net/projects/bric1936).[22] Intracranial volume (ICV) was measured using the Image Edit tool in the Analyze 9.0™.[16] WMH were visually rated by an experienced, neuroradiologist on the FLAIR and T_2-weighted images using the Fazekas scale,[23] with deep and periventricular WMH first 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 III, USA), all statistical tests being two-tailed, and p values <0.05 being considered significant. BP measures at wave 1 and 2 were compared using paired t-tests and health conditions at wave 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 which are known or proposed predictors of WMH, BP or blood velocity parameters were included in the analysis: age in days at MRI, sex, BMI, and self-reported history of ischemic heart disease, stroke, PVD, other circulatory disorders, diabetes, hypertension, smoking, and hypercholesterolemia. We modelled the association between BP, ICA blood velocity parameters and WMH in stages, each individually and then all three elements together. We tested associations with and without history of hypertension included in the models (to avoid over-fitting) – as there was little difference in the results whether hypertension was included or not, 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 (FDR). We tested both WMH volume and Fazekas score and whether the associations differed between hypertensive and non-hypertensive subjects using Pearson bivariate analysis. As 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.

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Results

Subjects

Of the 700 subjects with brain MRI, six 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 wave 1 and wave 2: hypertension (37% to 48.7%), ischaemic heart disease (21.7% to 27.3%), diabetes (6.6% to 11.0%), stroke (4.4% to 6.9%), hypercholesterolemia (33.3% to 41.4%), PVD (37.5% to 42.1%) and other circulatory problems (13.6% to 17.6%, all $p<0.00$). There was no significant difference in BMI between wave 1 and 2. ICA stenosis >50% was only present (on either side) in 2.9% and internal carotid occlusion on either side in one patient each (0.3%).

We found similar changes from wave 1 to wave 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 systolic BP (Table 1), but mean and diastolic BP 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 mm^3, or 0.83±0.90% of ICV. 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 1, Table 2, Supplementary Figure S1). Full results, including covariate effects, are reported in Supplementary Table S3. There were numerous relatively weak associations between BP and ICA velocities, but in general, these were strongest and most consistent for lower diastolic BP and higher ICA pulsatility index (with few associations for systolic BP), 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 diastolic BP (all $p<0.001$) and higher pulse pressure (all $p<0.004$). Higher ICA diastolic velocity was associated with lower diastolic BP ($\beta=-0.09$, $p=0.024$) and lower mean BP ($\beta=-0.08$, $p=0.029$), but no other BP measure. Higher ICA pulsatility index was associated with higher systolic BP ($\beta=0.08$, $p=0.04$), lower diastolic BP ($\beta=-0.19$, $p<0.001$) and higher pulse pressure ($\beta=0.10$, $p=0.008$). Higher ICA resistivity index was associated with lower diastolic BP ($\beta=-0.18$, $p<0.001$) 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 (Supplementary 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 scores. At wave 1, higher mean BP ($\beta=0.09$, $p=0.02$, Figure 1, Table 3, Supplementary Figure S1) and diastolic BP ($\beta=0.08$, $p=0.04$) were weakly associated with larger WMH volume, with similar but weaker associations at wave 2. Higher Fazekas scores (Supplementary Table S4) were significantly associated with higher systolic BP (wave 1: $\beta=0.12$, $p=0.002$), mean BP (wave 1: $\beta=0.13$, $p=0.001$) and diastolic BP (wave 1: $\beta=0.11$, $p=0.003$), with similar but weaker associations at wave 2. No association was found between WMH measures (WMH volume or Fazekas) and pulse pressure or variability (Supplementary Table S2). All the significant associations remained significant after correction for FDR.

ICA blood velocity measures and WMH measures

Without accounting for BP measures (Figure 1, Table 3), larger WMH volume was associated with higher ICA pulsatility index ($\beta=0.09$, $p=0.016$), and higher Fazekas scores

(Supplementary 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 1, Supplementary Table 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 FDR correction. No association was found between WMH and other ICA blood velocity measures, but those with history of hypertension had larger WMH volumes (Table 3, β=0.13, p<0.001) and higher Fazekas scores (Supplementary Table S4, β=0.16, p<0.001).

Sensitivity analyses

In hypertensive subjects, the associations between BP, ICA parameters and WMH were slightly stronger than in normotensive subjects, but there were no differences in direction of association or other features (Supplementary Table S6). After converting standardized to unstandardized betas, for every 1 year increase in age there was approximately a 2.43 cm^3 increase in WMH volume. Additionally, for every additional individual diagnosis of hypertension, there was approximately a 3.47 cm^3 increase in WMH volume.

Discussion

We investigated associations between BP parameters measured longitudinally, ICA velocity parameters and WMH in about 700 community-dwelling individuals aged around 73. Higher systolic, mean and diastolic BPs 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* diastolic BP, was associated with WMH (Figure 1). All associations remained significant after correcting for multiple testing and whether or not ‘hypertension’ was included in the model. Thus the association between BP measures and WMH is different to 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 co-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 one year increase in age was associated with 2.43 ml increase in WMH volume, and ‘hypertension’ (vs 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 two waves, and were living in the community. The proportion with cardiovascular conditions and risk factors increased over the three years, with hypertension increasing from 38% to 50% consistent with previous studies.[8-10,24-28] The association between higher systolic, mean and diastolic BP and WMH is consistent with many previous studies.[3,4,8,29-32]

Some studies[9,10] have reported associations between WMH and ICA or MCA pulsatility index, but no previous studies examined associations between BP, ICA parameters and WMH simultaneously or longitudinally, or the role of *falling* diastolic BP 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,[11] in hypertensive subjects amongst 1460 community-dwelling subjects,[8] in 1587 Framingham subjects,[33] 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. Pulse wave velocity assessed 10 years later in 303 elderly subjects, but only in one white matter tract.[36] Lower aortic diastolic BP, increased aortic pulse pressure and increased MCA pulsatility index were associated with WMH in 100 stroke patients of wide age range,[10] similar to our findings and suggesting a co-association rather than a direct association. The powerful effects of age on many biological processes is difficult to correct statistically: in addition to our 2.43 ml/year increase in WMH, MCA flow velocity falls by 0.2 cms^{-1} per year increase in age (p=0.045) and by 3.75 cms^{-1} per point increase in WMH Fazekas score (p=0.004). Consequently, MCA PI 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 two 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, systolic BP did not change between waves 1 and 2 but diastolic BP fell and consequently pulse pressure increased. Lower diastolic BP, higher pulse pressure and higher ICA pulsatility index, mean and diastolic velocity were consistently associated, but systolic BP associations were generally inconsistent and weak. After adjusting for BP, larger WMH volume was associated with higher ICA pulsatility index and lower diastolic BP. The pathway from BP to WMH is therefore through falling diastolic BP, 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 systolic BP is most prominent, are contrary to the direct path of BP transmission to the brain via the carotid arteries where *lower* diastolic BP is the associated variable. This might suggest that diastolic BP was falling below an acceptable perfusion pressure to result in WMH, but the diastolic BP values (mean 78.1, SD 9.68, Table 1) do not suggest that 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; five ICA blood velocity measures averaged across right and left and two measures of WMH recorded at mean age 73. 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 LBC1936[15,16] 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.[31] We calculated mean velocity to avoid errors in machine-calculated values which

may have under-or over-estimated 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 co-association acting through increased arterial stiffness has implications for strategies to prevent WMH progression, their cognitive and physical consequences. Treatment of hypertension is important for stroke prevention, but there is less evidence that it reduces WMH progression[41,42] (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 impacts 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.

Conclusion

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 diastolic BP, 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 co-associations. Determining if 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Novelty and Significance

What is new?

- Blood pressure (BP) and brain vascular damage seen as white matter hyperintensities (WMH) appear to be linked indirectly through a shared co-association with increasing arterial stiffness.
- The complete pathophysiological pathway from BP via internal carotid artery (ICA) velocity parameters to WMH has not been studied before.
- Narrow age-range sample allows differentiation of direct from indirect BP effects.

What is relevant?

- Hypertension increases with age and is a major risk factor for WMH.
- Advancing age strongly influences WMH.

Summary

Increased pulse pressure, secondary to *falling* diastolic BP, is associated with increased ICA pulsatility index, which in turn is associated with WMH at age 72. Further research is required to determine if methods to reduce arterial stiffness, as well as to reduce BP, prevent WMH formation or progression and their cognitive and physical consequences.

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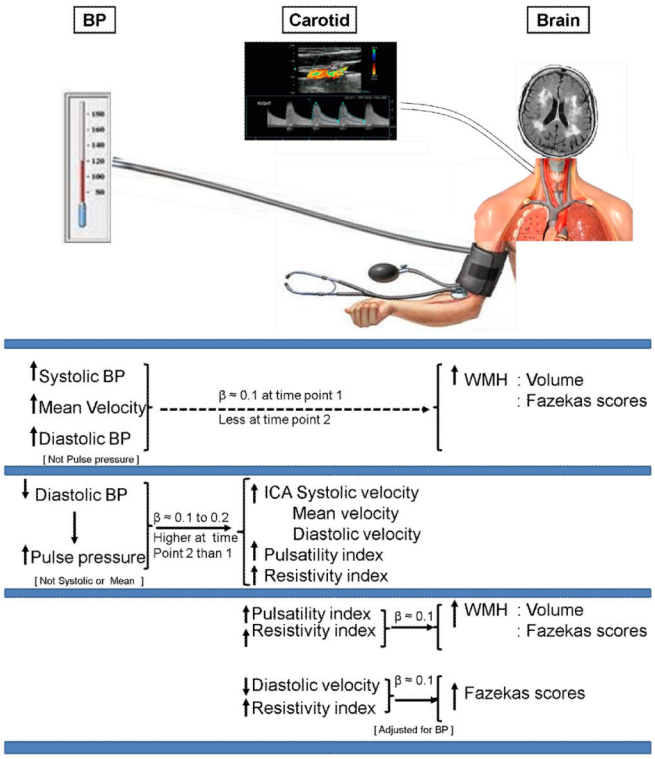

Figure 1. Summary of the associations between measures of BP, of ICA blood velocity parameters and of WMH (volume and Fazekas scores).

BPs were measured at waves 1 (time point 1), mean age 69.6±0.83, and 2 (time point 2), mean age 72.6±0.71; ICA velocity parameters and WMH were measured at wave 2. Models accounted for all covariates.

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Table 1

Descriptive statistics for measures of: BP, blood velocity in the ICA, WMH measures, demographic and health conditions

		Mean (SD)	
Parameter Assessed	**Measures**	**Wave 1 (N=1091)**	**Wave 2 (N=694)**
BP measures	Peak Systolic BP (mmHg)	149.45 (18.96)	148.69 (18.95)
	Mean BP (mmHg)	104.00 (11.81)	**102.00 (11.27)****
	End diastolic BP (mmHg)	81.45 (10.17)	**78.1 (9.68)****
	Pulse pressure (mmHg)	68.00 (14.91)	**71.34 (18.94)****
Measures of blood velocity in the ICA	Peak Systolic velocity (cm s^{-1})		59.91 (20.33)
	Mean velocity (cm s^{-1})		32.53 (10.59)
	End Diastolic velocity (cm s^{-1})		18.85 (7.09)
	Pulsatility index		1.27 (0.26)
	Resistivity index		0.66 (0.40)
WMH and related measures	White matter hyperintensities volume (cm^3)		12.05 (12.84)
	Intracranial volume (cm^3)		1450.97 (140.57)
	Percentage of White matter lesions in ICV		0.83 (0.90)
	Total Fazekas scores, median (IQR)		2.00 (1.00)
	Deep Fazekas scores, median (IQR)		1.00 (0)
	Periventricular Fazekas scores, median (IQR)		1.00 (1)
Demographic and health conditions	% men	53	53
	Age in years, mean (SD)	69.57 (0.83)	72.55 (0.71)
	Body mass index, mean (SD)	27.83 (4.38)	27.98 (4.50)
	History of hypertension (%)	37.10	**48.70** †
	History of ischemic heart disease (%)	21.70	**27.30** †
	History of diabetes (%)	8.60	**11.00** †
	History of stroke (%)	4.40	**6.90** †
	History of smoking (%)		56.10
	History of hypercholesterolemia (%)	33.30	**41.40** †
	History of peripheral vascular diseases (%)	37.50	**42.10** *
	Problems with blood circulation (%)	13.60	**17.60** *

Measures changed significantly from wave 1 to 2:

* $p<0.05$,

† $p<0.001$

Table 2

Association between measures of BP and ICA blood velocity parameters.

Values are standardized β (*p* value, *FDR correctedpvalues*) for the sitting BP measures predicting ICA blood velocity measures after accounting for covariates. See Supplementary Table S3 for full covariate effects.

	Blood velocity in the ICA				
BP Measures	**Systolic velocity**	**Mean velocity**	**Diastolic velocity**	**Pulsatility index**	**Resistivity index**
Wave 1					
Systolic BP	0.06 (0.141,*0.256*)	0.04 (0.285,*0.407*)	0.01 (0.76,*0.80*)	0.04 (0.335,*0.447*)	0.04 (0.256,*0.394*)
Mean BP	−0.04 (0.245,*0.394*)	−0.02 (0.647,*0.711*)	0.02 (0.533,*0.627*)	**−0.11 (0.003,*0.009*)** *	−0.08 (0.054,*0.111*)
Diastolic BP	**−0.13 (0.001,*0.003*)** *	−0.07 (0.068,*0.120*)	0.03 (0.423,*0.529*)	**−0.24 (<0.0001,*<0.0005*)** *	**−0.18 (<0.0001,*<0.0005*)** *
Pulse pressure	**0.15 (<0.0001,*<0.0005*)** *	**0.09 (0.011,*0.028*)** *	−0.01 (0.887,*0.88*)	**0.19 (<0.0001,*<0.0005*)** *	**0.17 (<0.0001,*<0.0005*)** *
Wave 2					
Systolic BP	0.02 (0.536,*0.596*)	−0.01 (0.757,*0.850*)	−0.06 (0.114,*0.147*)	**0.11 (0.004,*0.014*)** *	**0.10 (0.013,*0.022*)** *
Mean BP	**−0.10 (0.009,*0.018*)** *	**−0.10(0.008,*0.018*)** *	−0.08 **(0.029,*0.031*)** *	−0.04 (0.349,*0.400*)	−0.01 (0.722,*0.75*)
Diastolic BP	**−0.20 (<0.0001,*<0.0005*)** *	**−0.17 (<0.0001,*<0.0005*)** *	**−0.09 (0.024,*0.029*)** *	**−0.18 (<0.0001,*<0.005*)** *	**−0.12 (0.002,*0.003*)** *
Pulse pressure	**0.13 (<0.0001,*<0.004*)** *	**0.11 (0.004,*0.010*)** *	0.05 (0.217,0.271)	**0.12 (0.002,*0.007*)** *	**0.10 (0.012,*0.022*)** *

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

Table 3

Association between WMH volume and measures of BP and ICA blood velocity (standardized β (*p* value, *FDR correctedpvalues*)).

Models accounted for all covariates.

Predicting WMH volume from measures of BP				
		Covariates		
Measures of BP at waves 1 or 2	**BP Measures**	**ICV**	**Sex**	**Age in days**
Systolic BP, wave 1	**0.08 (0.043**,*0.057*)	**0.12 (0.021)**	0.08 (0.126)	0.15 (<0.0001)
Systolic BP, wave 2	*0.06 (0.113*,*0.248)*	0.12 (0.019)	0.08 (0.123)	0.14 (<0.0001)
Mean BP, wave 1	***0.09 (0.021***,*0.057*)	**0.11 (0.023)**	0.08 (0.118)	**0.15 (<0.0001)**
Mean BP, wave 2	0.06 (0.144,*0.248*)	0.12 (0.02)	0.08 (0.131)	0.14 (<0.0001)
Diastolic BP, wave 1	**0.08 (0.036**,*0.057*)	**0.11 (0.025)**	0.08 (0.121)	**0.15 (<0.0001)**
Diastolic BP, wave 2	0.04 (0.306,*0.306*)	0.12 (0.021)	0.08 (0.123)	0.14 (<0.0001)
Pulse pressure, wave 1	0.04 (0.249,*0.249*)	0.12 (0.02)	0.07 (0.142)	0.14 (<0.0001)
Pulse pressure, wave 2	0.05 (0.186,*0.248*)	0.12 (0.021)	0.08 (0.131)	0.14 (<0.0001)

Predicting WMH volume from measures of ICA velocity					
		Covariates			
Measure of ICA velocity at wave 2	**ICA velocity measures**	**ICV**	**Sex**	**Age in days**	**Hypertension**
Systolic velocity	0.04 (0.343,*0.428*)	0.13 (0.011)	0.09 (0.085)	0.14 (<0.0001)	0.13 (<0.0001)
Mean velocity	0.00(0.990,*0.990*)	0.13 (0.011)	0.09 (0.086)	0.13 (<0.0001)	0.13 (<0.0001)
Diastolic velocity	−0.05 (0.178,*0.283*)	0.13 (0.012)	0.09 (0.075)	0.13 (0.001)	0.13 (0.001)
Pulsatility index	**0.09 (0.016,*0.08*)**	**0.12 (0.014)**	**0.10 (0.047)**	**0.13 (<0.0001)**	**0.12 (0.002)**
Resistivity index	0.07 (0.054,*0.135*)	**0.12 (0.015)**	**0.09 (0.066)**	**0.14 (<0.0001)**	**0.13 (0.001)**

Note: Dependent variables were measures of WMH while independent variables were measures of ICA 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.