Circulating Inflammatory Markers Are Associated With Magnetic Resonance Imaging-Visible Perivascular Spaces But Not Directly With White Matter Hyperintensities

Benjamin S. Aribisala, PhD; Stewart Wiseman, BSc; Zoe Morris, FRCP; Maria C. Valdés-Hernández, PhD; Natalie A. Royle, BSc; Susana M. Maniega, PhD; Alan J. Gow, PhD; Janie Corley, BSc; Mark E. Bastin, PhD; John Starr, MD; Ian J. Deary, PhD; Joanna M. Wardlaw, MD

Background and Purpose—White matter hyperintensities (WMH) and perivascular spaces (PVS) are features of small vessel disease, found jointly on MRI of older people. Inflammation is a prominent pathological feature of small vessel disease. We examined the association between inflammation, PVS, and WMH in the Lothian Birth Cohort 1936 (N=634).

Methods—We measured plasma fibrinogen, C-reactive protein, and interleukin-6 and rated PVS in 3 brain regions. We measured WMH volumetrically and visually using the Fazekas scale. We derived latent variables for PVS, WMH, and Inflammation from measured PVS, WMH, and inflammation markers and modelled associations using structural equation modelling.

Results—After accounting for age, sex, stroke, and vascular risk factors, PVS were significantly associated with WMH (β=0.47; P<0.0001); Inflammation was weakly but significantly associated with PVS (β=0.12; P=0.048), but not with WMH (β=0.02; P=NS).

Conclusions—Circulating inflammatory markers are weakly associated with MR-visible PVS, but not directly with WMH. Longitudinal studies should examine whether visible PVS predate WMH progression and whether inflammation modulators can prevent small vessel disease. (Stroke. 2014;45:605-607.)

Key Words: aging ■ inflammation ■ leukoaraiosis ■ leukoencephalopathies ■ magnetic resonance imaging

The pathogenesis of small vessel disease (SVD) is poorly understood. It is thought to result from arteriolosclerosis in the penetrating arterioles leading to ischemia with diffuse rarefaction, necrosis, and cavitation in the subcortical tissues seen as white matter hyperintensities (WMH) and lacunes on MRI. Although perivascular inflammation is a prominent well-established pathological feature in WMH and lacunar stroke, the nature of inflammation and its role in the pathogenesis of SVD is uncertain.

Perivascular spaces (PVS), another marker of SVD, are thought to be associated with elevated plasma inflammatory markers in older subjects and in patients with small subcortical stroke. The association between plasma markers of inflammation and WMH is less clear. We tested if inflammatory markers had a direct and potentially causal relationship with WMH, or if any relationship was via an association with PVS.

**Subjects**
Participants are members of the Lothian Birth Cohort 1936 (LBC1936), all born in 1936. At mean age of 73 years, inflammatory markers (N=866) were measured and brain MRI was performed (N=700). Participants provided demographic information, medical history, and informed consent.

**Measurement of Inflammatory Markers**
C-reactive protein (CRP) and interleukin-6 (IL-6) were analyzed using high-sensitivity ELISA (R&D Systems, Oxford, United Kingdom). Fibrinogen was measured using an automated Clauss assay (TOPS coagulometer; Instrumentation Laboratory, Warrington, United Kingdom). See the online-only Data Supplement for details.

**Brain MRI**
Brain MRI data were acquired on a 1.5-T GE Signa Horizon HDx scanner (GE, Milwaukee, WI) and included T1-W, T2-W, T2*-W, and fluid attenuated inversion recovery brain imaging.

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WMH were segmented using MCMVXVI\(^\text{TM}\) and visually rated by a neuroradiologist on fluid attenuated inversion recovery images using the Fazekas scale.\(^1\) Another neuroradiologist crosschecked 20\%. The intraclass correlation coefficient was 0.96. Intracranial volume was extracted using Analyze 9.0.

PVS were rated in the hippocampus, basal ganglia, and centrum semiovale. Twenty percent were crosschecked by another neuroradiologist. Intra- and interrater \(\kappa\) statistics ranged from 0.68 to 0.90. See the online-only Data Supplement for details.

### Statistical Analyses

Bivariate associations were assessed between markers of inflammation, WMH, PVS, and covariates using Pearson correlation implemented in IBM SPSS version 19.0 (New York, NY). Covariates were sex, age at scanning, and history of cardiovascular disease, diabetes mellitus, hypertension, smoking, hypercholesterolemia, and stroke.

Multivariate associations were investigated using structural equation modelling,\(^1\) implemented in Amos 18.0.0 (Amos Development Corporation, FL; see the online-only Data Supplement for details). This allowed derivation of latent variables for WMH, PVS, and inflammation (WMH, PVS, and Inflammation, respectively) and also the assessment of relationships between latent variables while including covariates.

### Results

Of the 700 subjects who underwent brain MRI, 66 had incomplete data, reducing the final sample to 634 (Table I in the online-only Data Supplement). Almost half of the participants had a history of hypertension, smoking, or hypercholesterolemia, whereas 11\% had diabetes mellitus and 6.9\% had a history of stroke.

In bivariate correlation analysis (Table II in the online-only Data Supplement), all measures of WMH (ie, %WMH volume in intracranial volume, Fazekas periventricular, and Fazekas deep WMH scores) were significantly associated with PVS (in the hippocampus, basal ganglia, and centrum semiovale; \(r\) range, 0.11–0.52; \(P <0.001\)). No significant association was found between WMH measures and inflammation markers. Centrum semiovale PVS were significantly associated with CRP (\(r=0.10; P=0.010\)) but not fibrinogen or IL-6. All \(P\) values were Bonferroni corrected to account for multiple comparisons.

Multivariate analysis using structural equation modelling showed that PVS was significantly associated with WMH (\(\beta=0.47; P=0.0001\)), accounting for \(\approx 22\%\) variation in WMH (Figure 1). Inflammation was weakly but significantly associated with WMH (\(\beta=0.13; P=0.048\)), explaining 1.6\% of the variation in WMH (Figure 2). There was no significant association between Inflammation and WMH (Figure 3).

### Discussion

We demonstrate a strong association between increased numbers of visible PVS and increased amounts of WMH in adults aged 71 to 74 years. We demonstrate that variation in PVS accounted for \(\approx 22\%\) of the variation in WMH. However, despite previous reports of raised plasma inflammatory markers in subjects with SVD,\(^3\)\(^1\)\(^2\) we found only a weak association between inflammatory markers and PVS and no association between inflammatory markers and WMH. The narrow age cohort may have allowed us to unmask several relationships...
that are actually coassociations rather than direct associations as suggested in wider age range cohorts.

The weak association between Inflammation and PVS is consistent with the hypothesis that inflammation influences SVD through effects on the small perforating arterioles, which in turn precipitate WMH, but substantially more work is required to determine the direction and strength of the association.

The lack of association between inflammatory markers and WMH contrasts with some previous studies that found associations between CRP (n=6518),4,12 or IL-6 (n=3644),12 and WMH. However, it agrees with other studies (n=1699),5,13–15 a total of 2333 subjects, including the present study, not showing an association between CRP and WMH. Fewer studies have addressed associations between IL-6 or fibrinogen and WMH or PVS. Studies of inflammation and WMH are dominated by the Cardiovascular Health Study,12 which contributes two thirds of the data on CRP and all of the data on IL-6 and WMH. The study11 used MR images acquired from 1992 to 1994, which may have been less sensitive to WMH compared with current scanners; the wider age cohort may have suggested an inflammation–WMH association that was, in part, a residual age coassociation despite correction for age.

The strengths of the present work include the use of both volumetric and visual WMH scores, the use of structural equation modelling for a robust multivariate analysis, the cohort with a narrow age range, and little ethnic diversity to reduce confounding. Weaknesses include the relative health of the participants (about half were hypertensive) and the limited number of inflammatory variables examined (but the 3 used are well understood and key to pathological processes).

Future studies should consider examining inflammatory markers in younger subjects with SVD, because they may show a stronger differential inflammatory plasma profile. Studies should also examine direct evidence of inflammation in the brain.

Acknowledgments

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Disclosures

None.

References

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Circulating inflammatory markers are associated with MR visible Perivascular Spaces but not directly with White Matter Hyperintensities

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3Scottish Imaging Network, A Platform for Scientific Excellence (SINAPSE)
4Department of Computer Science, Lagos State University, Nigeria
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6Department of Psychology, University of Edinburgh, UK
7Geriatric Medicine Unit, University of Edinburgh, UK

Measurement of Inflammatory Markers

Bivariate Statistics

Multivariate Statistics using Structural Equation Modelling
Measurement of Inflammatory Markers

C-reactive protein (CRP) and interleukin 6 (IL6) were analysed at the University of Glasgow using high sensitivity ELISA from R&D Systems (Oxford, UK). For IL-6, the minimum detectable dose (MDD) ranged from 0.016-0.110 pg/mL (mean=0.039 pg/mL). The intra-assay coefficient of variation (CV) ranged from 6.9% to 7.8%, while the inter-assay CV ranged from 6.6% to 9.6%. For CRP, the MDD ranged from 0.005-0.022 ng/mL (mean=0.010 ng/mL). The intra-assay CV ranged from 3.8% to 8.3%, while the inter-assay CV ranged from 6.0% to 7.0%. Fibrinogen was measured using an automated Clauss assay (TOPS coagulometer, Instu-mentation Laboratory, Warrington, UK) with a CV of 3.69% [1].

Measurement of Perivascular Spaces

PVS were visually rated by a neuroradiologist on all slices through the hippocampus, basal ganglia (BG) and centrum semiovale (CS) using a validated method [2], as 0=no PVS, 1=1 to 10 PVS, 2=11 to 20 PVS, 3=21 to 40 and 4=40 and above PVS. The left and right sides were rated separately and then added together to provide a ‘total brain’ score. 20% were cross checked by another neuroradiologist. Intra- and inter-rater kappa statistics ranged from 0.70-0.87, 0.80-0.90, and 0.68-0.75 for hippocampus-PVS, BG-PVS, and CS-PVS respectively. All image analysis was performed blind to clinical data.

Bivariate Statistics

Supplementary Table I shows the descriptive statistics. The total median (and interquartile range ) Fazekas score was, 2.0 (1.0), range 0 to 6 (periventricular median score was 1.0 (1.0), range 0 to 3, and deep median score was 1.0 (0), range 0 to 3). The median and interquartile range PVS scores were 0 (0), range 0 to 2 in the hippocampus, 1.0 (1.0), range 0 to 4 in the BG, and 2.0 (1.0), range 0 to 4 in the CS. Inflammatory marker levels are given in Supplementary Table I.

Bivariate associations were assessed between markers of inflammation, WMH, PVS and covariates using Pearson correlation implemented in SPSS 19.0. Covariates were sex, age in days at scanning, and history of cardiovascular disease, diabetes, hypertension, smoking, hypercholesterolemia and stroke. Note that although WMH, CRP and IL-6 were not normally distributed, their associations with other variables using both Pearson and Spearman correlations gave nearly identical results; therefore as the structural equation modelling (SEM) approach [3] used here uses Pearson, we used the Pearson correlations for bivariate associations for consistency.

Supplementary Table II presents the bivariate association between markers of Inflammation, WMH and PVS measures. The main results have been presented in the main text. As expected, Fibrinogen, CRP and IL-6 were all significantly positively correlated with each other as were all measures of WMH with each other and all measures of PVS with each other.

Correlations between the covariates and inflammation markers, WMH and PVS, are presented in Supplementary Table III. History of hypertension and of stroke correlated consistently with WMH.
History of smoking correlated consistently with inflammation (r range 0.08 to 0.16, P<0.001). Advancing age (even within the narrow range included) was associated with declining fibrinogen (r = -0.13, P<0.001), but not CRP or IL-6, and increase in WMH (r=0.14, P<0.001). Sex was significantly associated with Fazekas deep score (r=0.11, P=0.003) with women having higher Fazekas scores than men. Other health covariates (diabetes, hypercholesterolaemia and cardiovascular disease histories) showed no significant correlation with markers of inflammation, WMH or PVS.

Multivariate Statistics using Structural Equation Modelling

In statistical modelling, latent variables are employed when the parameter of interest is inadequately measured by a single variable. Latent variables are estimated based on the shared common variance between a set of measured indicator variables, and this allows the exclusion of measurement errors when estimating the contribution that each measured variable makes to the latent variable [4, 5]. Structural equation models (SEM), used in this study, simultaneously provides estimates of such latent variables (the measurement model), and the correlations and uni-directed paths (regression parameters, which may be thought of like standardised, partial beta weights) between latent variables (the structural model). The SEM is conventionally represented by a diagram as in the figures presented here where the rectangular boxes each represent measured observations, e.g. CRP or WMH volume. Each circle or ellipse represents a latent construct, e.g. ‘inflammation’ or ‘PVS’, which is a weighted combination of the correlated individual measured variables. Paths in the diagrams that are single-headed arrows represent hypothesised causal pathways from a predictor variable to the outcome variable, and double headed arrows represent correlations. Solid arrows represent associations that are statistically significant at p <0.05 while dashed arrows represent associations that are not significant at p <0.05. Numbers adjacent to paths may be squared to obtain the shared variance between adjacent variables. The numbers on the arrows pointing from the latent to the measured variables, called the factor loading or correlation coefficient, represent the strength of the association between the measured and latent variables, +/- 1 indicate the strongest association. Thick arrows pointing to the measured variables mean that that error term was accounted for in the modelling and the numbers adjacent represent the r² which is the square of the factor loading.

The three measurement models of ‘inflammation’, ‘WMH’ and ‘PVS’ all fitted well (model fit statistics are presented in figure legends). The factor loadings for the latent variables of ‘inflammation’, ‘WMH’ and ‘PVS’ were moderate to large, indicating that the measurement models were good for the three latent traits. The standardised path values were all large (shown in Supplementary Figures I to III) indicating that the latent variables are robust and account for between approximately 20% and 88% of variance in the measured variables in all models.

Model fit parameters are shown in the legends: the maximum modification index (Max MI, which indicates the degree of greatest local strain within the model in terms of a potential reduction in model chi square); the comparative fit index, (CFI, ≥0.90 indicates acceptable fit); and the root mean square error of approximation (RMSEA, <0.06 indicates acceptable fit).

All models were estimated using full information maximum likelihood estimation. Model fit was evaluated based on commonly adopted cut-off points for the Root Mean Square Error Approximation (RMSEA), Tucker-Lewis Index (TLI), Comparative Fit Index (CFI), incremental Fit index (IFI) and the Standardized Root Mean Square of <0.06, >0.90, >0.90, >0.90 and <0.06 respectively [3]. Model modifications were based on the standardized residual covariance < 1.96. Associations were modelled using a stepwise approach. The first set of models included only the measures of inflammation markers & PVS measures, inflammation markers & WMH measures,
PVS measures & WMH measures or inflammation markers & PVS measures & WMH measures (Supplementary Figure I). Then, demographic variables were introduced (Supplementary Figure II). All health variables were then introduced (Supplementary Figure III), and the models were modified using the standardized residual covariance matrices to produce the final models (Figures 1 to 3) which produced satisfactory model fits.

All imaging features were defined according to the STandards for ReportIng Vascular Changes on NEuroimaging (STRIVE) v1 [6].
**Supplementary Table I:** Descriptive statistics for markers of inflammation, measures of WMH, PVS, demographic and health conditions

<table>
<thead>
<tr>
<th>N=634</th>
<th>Measures</th>
<th>Mean(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Markers of Inflammation</strong></td>
<td>CRP</td>
<td>2.94(5.97)</td>
</tr>
<tr>
<td></td>
<td>Fibrinogen</td>
<td>3.34(0.60)</td>
</tr>
<tr>
<td></td>
<td>IL6</td>
<td>2.00(1.74)</td>
</tr>
<tr>
<td><strong>Measures of PVS</strong></td>
<td>Hippo-PVS</td>
<td>0.25(0.45)</td>
</tr>
<tr>
<td></td>
<td>BG-PVS</td>
<td>1.43(0.58)</td>
</tr>
<tr>
<td></td>
<td>CS-PVS</td>
<td>2.07(0.74)</td>
</tr>
<tr>
<td><strong>WMH and related measures</strong></td>
<td>WMH (mm3)</td>
<td>12186.18(13289.57)</td>
</tr>
<tr>
<td></td>
<td>ICV (mm3)</td>
<td>1442352.06(142201.34)</td>
</tr>
<tr>
<td></td>
<td>% WMH in ICV</td>
<td>0.85(0.92)</td>
</tr>
<tr>
<td></td>
<td>Fazekas Periventricular scores, median (IQR)</td>
<td>1.00(1.00)</td>
</tr>
<tr>
<td></td>
<td>Fazekas Deep scores, median (IQR)</td>
<td>1.00(0.00)</td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
<td>Age in years, mean (SD)</td>
<td>72.5(0.72)</td>
</tr>
<tr>
<td></td>
<td>% men</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td><strong>Health conditions</strong></td>
<td>History of hypertension (%)</td>
<td>48.70</td>
</tr>
<tr>
<td></td>
<td>History of diabetes (%)</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>History of stroke (%)</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>History of smoking (%) current or ever smoked</td>
<td>56.1</td>
</tr>
<tr>
<td></td>
<td>History of hypercholesterolemia (%)</td>
<td>41.4</td>
</tr>
</tbody>
</table>

Note. CRP=C-reactive Protein, IL6=Interleukin 6, hippo=Hippocampus, BG=Basal Ganglia, CS=Centrum Semiovale, PVS=Perivascular Spaces, WMH=White Matter Hyperintenities, ICV=Intracranial Volume, IQR=Interquartile Range, SD=Standard Deviation
**Supplementary Table II:** Bivariate Correlations (p values) within and between markers of Inflammation, WMH and PVS measures; Bonferroni corrected (N=634)

<table>
<thead>
<tr>
<th></th>
<th>CRP</th>
<th>Fibrinogen</th>
<th>IL6</th>
</tr>
</thead>
<tbody>
<tr>
<td>% WMH in ICV</td>
<td>0.00(0.97)</td>
<td>0.00(0.92)</td>
<td>0.02(0.54)</td>
</tr>
<tr>
<td>Fazekas Peri</td>
<td>0.00(0.99)</td>
<td>0.05 (0.21)</td>
<td>0.04(0.30)</td>
</tr>
<tr>
<td>Fazekas Deep</td>
<td>0.01 (0.74)</td>
<td>0.00(0.97)</td>
<td>0.02(0.57)</td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
<td>0.41 (&lt;0.001)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
<td>0.37(&lt;0.001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>% WMH in ICV</th>
<th>Fazekas Peri</th>
<th>Fazekas Deep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hippo-PVS</td>
<td>0.11(0.03)</td>
<td>0.21(&lt;0.001)</td>
<td>0.16(&lt;0.001)</td>
</tr>
<tr>
<td>BG-PVS</td>
<td>0.31(0&lt;0.001)</td>
<td>0.32(0&lt;0.001)</td>
<td>0.31(0&lt;0.001)</td>
</tr>
<tr>
<td>CS-PVS</td>
<td>0.18(0&lt;0.001)</td>
<td>0.23(0&lt;0.001)</td>
<td>0.19(&lt;0.001)</td>
</tr>
<tr>
<td>% WMH in ICV</td>
<td>0.72(&lt;0.001)</td>
<td>0.65(&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Fazekas Peri</td>
<td></td>
<td></td>
<td>0.52(&lt;0.001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PVS hippo</th>
<th>BG-PVS</th>
<th>CS-PVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>0.03(0.40)</td>
<td>0.01(0.86)</td>
<td>0.10(0.10)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.06(0.15)</td>
<td>0.05(0.24)</td>
<td>0.03(0.42)</td>
</tr>
<tr>
<td>IL6</td>
<td>0.02(0.58)</td>
<td>0.02(0.54)</td>
<td>0.09(0.22)</td>
</tr>
<tr>
<td>Hippo-PVS</td>
<td>0.25(&lt;0.001)</td>
<td>0.27(&lt;0.001)</td>
<td>0.40(&lt;0.001)</td>
</tr>
<tr>
<td>BG-PVS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: See note Table 1.
**Supplementary Table III:** Pearson bivariate and biserial (*) correlations (p values) between covariate risk factors, markers of inflammation, WMH and PVS measures

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age</th>
<th>Smoking*</th>
<th>Hypertension*</th>
<th>Diabetes*</th>
<th>Hypercholesterolaemia*</th>
<th>Cardiovascular Disease*</th>
<th>Stroke*</th>
</tr>
</thead>
<tbody>
<tr>
<td>% WMH in ICV</td>
<td>0.01(0.85)</td>
<td>0.14(&lt;0.001)</td>
<td>0.08(0.04)</td>
<td>0.13(0.001)</td>
<td>0.03(0.45)</td>
<td>0.07(0.05)</td>
<td>0.00(0.91)</td>
<td>0.08(0.03)</td>
</tr>
<tr>
<td>Fazekas Peri</td>
<td>0.01(0.85)</td>
<td>0.03(0.48)</td>
<td>0.06(0.12)</td>
<td>0.10(0.008)</td>
<td>0.02(0.65)</td>
<td>0.05(0.16)</td>
<td>0.00(0.92)</td>
<td>0.10(0.01)</td>
</tr>
<tr>
<td>Fazekas Deep</td>
<td>0.11(&lt;0.01)</td>
<td>0.08(0.04)</td>
<td>0.03(0.43)</td>
<td>0.19(&lt;0.001)</td>
<td>0.00(0.95)</td>
<td>0.03(0.43)</td>
<td>0.01(0.73)</td>
<td>0.08(0.04)</td>
</tr>
<tr>
<td>CRP</td>
<td>0.02(0.55)</td>
<td>0.04(0.24)</td>
<td>0.12(&lt;0.001)</td>
<td>0.10(0.01)</td>
<td>0.02(0.53)</td>
<td>0.01(0.76)</td>
<td>-0.03(0.43)</td>
<td>0.09(0.01)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.08(0.03)</td>
<td>-0.13(&lt;0.001)</td>
<td>0.16(&lt;0.001)</td>
<td>0.04(0.24)</td>
<td>0.02(0.65)</td>
<td>0.02(0.49)</td>
<td>0.01(0.75)</td>
<td>0.13(&lt;0.001)</td>
</tr>
<tr>
<td>IL6</td>
<td>-0.04(0.21)</td>
<td>0.04(0.24)</td>
<td>0.16(&lt;0.001)</td>
<td>0.06(0.08)</td>
<td>0.10(&lt;0.01)</td>
<td>0.00(0.95)</td>
<td>0.02(0.56)</td>
<td>0.09(0.01)</td>
</tr>
<tr>
<td>Hippo-PVS</td>
<td>0.03(0.38)</td>
<td>-0.18(&lt;0.001)</td>
<td>-0.05(0.21)</td>
<td>0.02(0.61)</td>
<td>-0.04(0.28)</td>
<td>0.03(0.41)</td>
<td>-0.01(0.72)</td>
<td>0.02(0.56)</td>
</tr>
<tr>
<td>BG-PVS</td>
<td>-0.02(0.68)</td>
<td>0.02(0.60)</td>
<td>-0.03(0.51)</td>
<td>0.11(0.01)</td>
<td>-0.03(0.39)</td>
<td>0.05(0.24)</td>
<td>-0.01(0.88)</td>
<td>0.01(0.76)</td>
</tr>
<tr>
<td>CS-PVS</td>
<td>0.00(0.99)</td>
<td>0.02(0.56)</td>
<td>-0.01(0.72)</td>
<td>0.03(0.41)</td>
<td>-0.04(0.30)</td>
<td>-0.05(0.19)</td>
<td>-0.05(0.19)</td>
<td>-0.03(0.49)</td>
</tr>
</tbody>
</table>

Abbreviations: See note Table 1.
Supplementary Figure 1: SEM of the association between measures of PVS and WMH using the basic model that included only the measures of PVS and measures of WMH.

Note. ‘PVS’=latent variable derived from measures of PVS, ‘WMH’=latent variable derived from measures of WMH. Models included only covariates that were significantly associated with WMH load or measures of PVS. BG=measured basal ganglia PVS, HIP=measured hippocampus PVS, CS=measured centrum semiovale PVS, high BP=history of hypertension, WMH v=% of WMH in ICV, Faz=Fazekas, Peri=Perivascular. Solid or thick arrows represent associations that are statistically significant at p < 0.05 while dashed arrows represent associations that are not significant at p < 0.05.
Supplementary Figure II: SEM of the association between measures of PVS and WMH. Model included age and Sex. Dotted lines are associations that are not significant.

Note. Abbreviations: See Figure 1.
Supplementary Figure III: SEM of the association between measures of PVS and WMH. Model included age and Sex and all health covariates (history of cardiovascular disease, diabetes, hypertension, smoking, hypercholesterolemia and stroke). Health variables that showed no significant association with WMH or PVS and that reduced model fit were removed from the model.

Note. Abbreviations: See Figure 1
References


