ORIGINAL RESEARCH

Associations of Vascular Risk Factors and APOE Genotype With Perivascular Spaces Among Community-Dwelling Older Adults

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BACKGROUND: Evidence suggests that enlarged perivascular spaces (PVSs) may represent a marker for cerebral small-vessel disease. We investigated whether vascular risk factors are correlated with visible PVS in older adults.

METHODS AND RESULTS: This population-based study included 530 participants (age ≥60 years) who were free from dementia and functional dependence, derived from the Swedish National study on Aging and Care in Kungsholmen (2001–2003). We collected data on demographics, vascular risk factors, and health conditions through interviews, clinical examinations, laboratory tests, and patient registers. Cerebral PVSs and white matter hyperintensities on magnetic resonance images were visually assessed with semiquantitative visual rating scales. Data were analyzed using the general linear regression models. After controlling for demographics and cardiovascular disease, very high blood pressure (≥160/100 mm Hg) was significantly associated with global PVS score (β-coefficient, 1.30; 95% CI, 0.06–2.53) and orthostatic hypotension was associated with PVS score in the basal ganglia (β-coefficient 0.37; 0.03–0.70), but the associations became non-significant when adjusting for white matter hyperintensity load. Orthostatic hypotension was significantly associated with global and lobar PVS scores in carriers but not in noncarriers of the APOE ε4 allele. Global or regional PVS score was not significantly associated with other traditional vascular risk factors such as smoking, diabetes mellitus, physical inactivity, and overweight or obesity.

CONCLUSIONS: This study provides limited evidence supporting a correlation of magnetic resonance imaging–visible PVS with traditional vascular risk factors in older adults. The association of orthostatic hypotension with lobar PVS among APOE ε4 carriers suggests that lobar PVS may be a marker for amyloid-associated small-vessel disease.

Key Words: APOE genotype ■ brain aging ■ magnetic resonance imaging ■ perivascular spaces ■ vascular risk factors

Perivascular spaces (PVSs) are virtual subpial spaces that can be widened to become visible on structural magnetic resonance imaging (MRI) under certain conditions. Most studies suggest that the number of MRI-visible PVSs increases with advancing age. In addition, a rather consistent association of enlarged PVSs with hypertension in older adults has been reported in several studies, although some studies have shown no association with hypertension. The relationship between MRI-visible PVSs and traditional vascular risk factors other than hypertension remains to be established.

Cerebral small-vessel disease (SVD) is a group of diagnoses, which are characterized on MRI as white matter hyperintensities (WMHs), lacunes, and cerebral microhemorrhages. Population-based studies have suggested a close correlation of visible PVSs with WMHs and lacunar infarcts; therefore, PVSs have been proposed as a marker for SVD. The predominant diagnoses of cerebral SVD are hypertensive arteriopathy and cerebral amyloid angiopathy. MRI markers for cerebral SVD such as cerebral microhemorrhages and enlarged PVSs in different brain regions are thought to reflect different pathologies. For
instance, cerebral microhemorrhages or PVSs in the basal ganglia region are supposed to indicate hypertensive arteriopathy, whereas the same markers in the lobar white matter are more likely to reflect cerebral amyloid angiopathy and other amyloid-dependent small-vessel disease.

What Are the Clinical Implications?
• Magnetic resonance imaging–visible PVSs are not a strong marker for hypertensive arteriopathy; however, lobar PVSs might be a marker for cerebral amyloid angiopathy and other amyloid-dependent small-vessel disease.

Nonstandard Abbreviations and Acronyms

| Acronym | Abbreviation                           | Full Form                                      |
|---------|---------------------------------------|------------------------------------------------|
| ICD-10  | International Classification of Diseases, 10th Revision |
| OH      | orthostatic hypotension               |                                               |
| MRI     | magnetic resonance imaging            |                                               |
| PVSs    | perivascular spaces                  |                                               |
| SNAC-K  | Swedish National Study on Aging and Care in Kungsholmen |
| SVD     | (cerebral) small-vessel disease       |                                               |
| WMHs    | white matter hyperintensities        |                                               |

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included in this study. In these people, a total of 15 brain regions in 6 participants were impossible to assess regarding PVSs because of large infarcts.6

SNAC-K was approved by the Regional Ethical Review Board in Stockholm, Sweden. Written informed consent was collected from all participants in the SNAC-K MRI sample.

**MRI Acquisition**

All participants were scanned on a Philips Intera 1.5 T system (Eindhoven, The Netherlands).6 For the visual assessment of PVSs, a T1-weighted sequence (Magnetization Prepared–Rapid Gradient Echo; TR 15, TE 7, FA 15) consisting of 150 1-mm axial slices without angulation, a fluid attenuation inversion recovery sequence (TR 6000, TI 1900, and TE 100, ETL 21, FA 90) of 20 5-mm slices with a 1-mm gap angled along the subcallosal line, and a PD/T2-weighted sequence (TR 3995, TE 18/90, ETL 6, FA 90) of 60 3-mm slices without gap or angulation were used. All of the images were reviewed on a clinical picture archiving and communication system (SECTRA, Linköping, Sweden).6

**Visual Assessment of PVS**

We used a visual rating scale to assess PVSs, taking into account the number, size, and location of the PVSs, as fully described elsewhere.6 For this study, we used only the score for the number of MRI-visible PVSs in different regions and not the size, because very few subjects had PVSs >4 mm.6 Briefly, the brain regions scored for PVSs were the cerebellum, midbrain (including upper part of pons), hippocampus, subinsular region (external capsule, claustrum, and extreme capsule), basal ganglia (medial to the external capsule and including thalamus), frontal lobe, and parieto-occipital lobe. MRI-visible PVSs in each region were counted and then scored as 0 (no visible PVSs), 1 (1–5 PVSs), 2 (6–10 PVSs), or 3 (>10 PVSs). The scores for different brain regions were then summed up to obtain a global semiquantitative measurement of visible PVSs, with a maximum score of 42. All of the images were assessed by an experienced clinical neuroradiologist (A.L.) without knowledge of the subjects’ clinical characteristics. The visual rating scale has an excellent weighted κ statistic of 0.77 for both intrarater and interrater reliability.6

**Visual Assessment of WMH**

The load of WMH was rated visually using a modified Scheltens scale.5,25 Briefly, the rating scale is the same as the original Scheltens scale, but the regionalization is different. First, the 2 hemispheres were rated separately. Second, the basal ganglia and thalami were divided into subinsular (external capsule, claustrum, and extreme capsule) and basal ganglia (medial to external capsule, including thalamus). Finally, the parietal and occipital lobes were combined into 1 region. Periventricular white matter hyperintensities were rated according to the original Scheltens scale. All assessments of WMHs were completed by a clinical neuroradiologist (A.L.) without knowledge of the subjects’ clinical characteristics. Twenty randomly selected subjects were reassessed after a 6-month interval. The intrarater reliability for WMHs was good, with a weighted κ statistic of 0.67.6

**Data Collection and Assessment**

From 2001 to 2003, data were collected through face-to-face interviews by trained nurses and clinical examinations by physicians, as previously reported.22,23 Data included demographic features, lifestyle and health behavioral factors, medical history, and use of medications. All medications were classified according to the Anatomical Therapeutic Chemical classification system. Peripheral blood samples were taken, and total cholesterol and APOE genotypes were measured at the university’s laboratory following standard methods. Information on health history for all participants was also available from the computerized National Patient Register, in which diseases were classified and coded according to the International Classification of Diseases, 10th Revision (ICD-10).

Education was measured as the maximum years of formal schooling, and was categorized into elementary or middle school, high school, and university or above. Smoking status was categorized as ever versus never smoking. Leisure-time physical activity was classified into inactivity versus activity (health-enhancing or fitness-enhancing activities). Weight and height were measured in light clothes with no shoes, and body mass index was calculated as mass (kg) divided by height (m) squared. After a minimum of 5 minutes’ rest in a quiet room, sitting arterial blood pressure was measured twice with a 5-minute interval on the left arm using a digital sphygmomanometer. The mean of the 2 readings was used in the analysis. Hypertension was defined as blood pressure ≥140/90 mm Hg or current use of antihypertensive agents (Anatomical Therapeutic Chemical codes C02, C03, and C07-C09). Stage 2 hypertension was defined as blood pressure ≥160/100 mm Hg. Orthostatic hypotension was defined as a decrease in systolic blood pressure of ≥20 mm Hg, or in diastolic blood pressure of ≥10 mm Hg, when standing up from resting in a supine position for 5 minutes. Diabetes mellitus was defined
as a self-reported history of diabetes mellitus, use of oral blood glucose-lowering drugs or insulin injection (Anatomical Therapeutic Chemical code A10), hemoglobin A1c >6.4%, or recorded in the patient register. High total cholesterol was defined as total cholesterol ≥6.22 mmol/L. High serum C-reactive protein was defined as >5 mg/L. Cardiovascular diseases included coronary heart diseases (ICD-10 codes: I20-I25), heart failure (I50), and atrial fibrillation (I49). APOE genotype was dichotomized as carriers, having at least 1 APOE ε4 allele versus noncarriers.

### Statistical Analysis

Characteristics of the study participants by brain MRI status were compared using t tests for continuous variables with normal distribution and chi-square tests for categorical variables. We used the general linear regression models to estimate β-coefficient (ie, difference in mean PVS score per 1-unit difference in the covariate) and 95% CI of global PVS score related to various vascular risk factors and APOE genotype. We used the model-based standard error estimates for β-coefficients in the general linear regression models because the Breusch-Pagan test (a test for heteroscedasticity) showed that the variance of residuals was constant. PVS scores in the lobar (frontal and parietal) and basal ganglia (basal ganglia and subinsular) regions were analyzed separately, in which multivariate general linear regression analysis was performed to estimate β-coefficient and 95% CI of regional PVS scores associated with vascular risk factors and APOE genotype. We tested the statistical interaction by simultaneously including the 2 factors and their cross-product term into the model. When a statistical interaction was detected, we further performed stratified analysis to verify the direction and magnitude of the interaction. In the main analysis, we controlled for age, sex, education, and cardiovascular disease. In further analysis, we controlled for global WMH score to assess whether the observed association with PVSs was present independent of WMH load. Stata 12.0 (StataCorp LP, College Station, TX) for Windows was used for all statistical analyses.

### Results

#### Characteristics of the Study Participants

The mean age of the 530 participants in the SNAC-K MRI study was 70.7 (SD, 9.1) years, and 58.9% were women. The SNAC-K MRI participants were younger, more likely to be men, and more educated than individuals in the non-MRI group (P<0.01) (Table 1). In addition, compared with people in the non-MRI group, the MRI participants were more physically active and were less likely to have diabetes mellitus, high C-reactive protein, and cardiovascular disease, but were more likely to have high total cholesterol (P<0.05) (Table 1).

#### Vascular Risk Factors, APOE Genotype, and Global PVS Score

Stage 2 hypertension (≥160/100 mm Hg) was significantly associated with a higher global PVS score when adjusted for demographic features and cardiovascular disease (Table 2). Similarly, both high systolic blood pressure (≥160 mm Hg) and high diastolic blood pressure (≥100 mm Hg) were significantly associated with a greater global PVS score in model 1; however, when WMH score was taken into consideration, the association remained statistically significant only with high systolic pressure (Table 2). There was no significant association of either OH or APOE ε4 allele with global PVS score.

#### Vascular Risk Factors, APOE Genotype, and Regional PVS Scores

Multivariate general linear regression analysis showed that OH was significantly associated with an increased PVS score in the basal ganglia region, but not in the lobar white matter; the association became statistically nonsignificant when WMH score was taken into account (Table 3). None of the other examined vascular risk factors or presence of the APOE ε4 allele was significantly associated with regional PVS score (Table 3).

#### Interactions of Vascular Risk Factors and APOE Genotype on PVS Scores

Statistically marginal or significant interaction was detected between OH and APOE ε4 allele for global PVS score (multivariable-adjusted P for interaction in model 2=0.052) and lobar white matter PVS score (multivariable-adjusted P for interaction in model 2=0.012). Further analysis stratified by APOE ε4 allele suggested that the association of OH with a greater global PVS score or a greater lobar PVS score was statistically significant among carriers, but not among noncarriers, of the APOE ε4 allele, especially when global WMH score was taken into consideration. No statistical interaction with APOE ε4 allele was found for any other vascular risk factors analyzed.

### Discussion

In this population-based study of nondisabled and nondemented older adults, we found that traditional cardiovascular risk factors, such as smoking, overweight, high total cholesterol, and diabetes mellitus, were not correlated with global PVSs or PVSs in the basal ganglia region nor in the lobar white matter. The observed associations of stage 2 hypertension...
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(≥160/100 mm Hg) with PVSs globally and of OH with higher PVS score in the basal ganglia region were largely attributable to the load of WMHs (Tables 2 and 3). Only very high systolic blood pressure (≥160 mm Hg) showed a marginal association with global PVS scores after adjusting for WMH load (Table 2). Similarly, we found no association between the APOE ε4 allele and MRI-visible PVSs. However, we detected an interaction between the APOE ε4 allele and OH, such that OH was associated with increased global and lobar PVS scores among APOE ε4 carriers, whereas among non-carriers of the APOE ε4 allele there was no association of OH with global and lobar PVS scores. This indicates a potentially modifying effect of APOE genotype on the relationship of OH with global and lobar PVSs.

Although MRI-visible PVSs are often considered a marker of cerebral SVD,\textsuperscript{3,6} research findings have been mixed with regard to whether enlarged PVSs are associated with traditional vascular risk factors. Indeed, several earlier studies have found a clear association between enlarged PVSs and different vascular risk factors, such as hypertension or high blood pressure,\textsuperscript{2,4,5,7,8} smoking,\textsuperscript{12} diabetes mellitus,\textsuperscript{26} and inflammatory markers.\textsuperscript{27,28} Notably, hypertension is the factor that has been most consistently associated with PVSs. However, there are also studies that did not find any association between global MRI-visible PVSs and vascular risk factors such as hypertension, smoking, or diabetes mellitus.\textsuperscript{3,9,10} In addition, most of the previous studies have not examined the effect of other SVD

Table 1. Characteristics of the Study Participants in the Total Sample and by Brain MRI Scan

| Characteristics* | Total Sample | Brain MRI data | P Value |
|------------------|--------------|----------------|---------|
|                  | (n=3363)     | No (n=2833)    | Yes (n=530) | |
| Age, y           | 74.3 (11.2)  | 75.0 (11.4)    | 70.7 (9.1)  | <0.01 |
| Female sex, n (%)| 2182 (64.9)  | 1870 (66.0)    | 312 (58.9)  | <0.01 |
| Educational level, n (%) |          |                |          | |
| Elementary/middle school | 590 (17.7) | 523 (18.67) | 66 (12.6)  | |
| High school      | 1651 (49.6) | 1405 (50.2)    | 246 (46.4) | |
| University or above | 1090 (32.7) | 873 (31.2)    | 217 (40.9) | <0.01 |
| Smoking status, n (%) |          |                |          | |
| Never            | 1568 (48.08)| 1324 (48.48)   | 244 (46.0) | |
| Former           | 1253 (38.4) | 1033 (37.8)    | 220 (41.5) | |
| Current          | 440 (13.49) | 374 (13.7)     | 66 (12.5)  | 0.269 |
| Physical inactivity, n (%) |          |                |          | <0.01 |
| Normal (~25)     | 1448 (47.7) | 1216 (48.5)    | 232 (43.9) | |
| Overweight (25–29.9) | 1196 (39.5) | 973 (38.8)    | 225 (42.5) | |
| Obesity (~30)    | 388 (12.8)  | 316 (12.6)     | 72 (13.6)  | 0.145 |
| Hypertension, n (%) | 2496 (75.0) | 2113 (75.5)   | 383 (72.3) | 0.113 |
| Blood pressure (mm Hg), n (%) |          |                |          | |
| <120/80          | 310 (9.4)   | 267 (9.6)      | 43 (8.1)   | |
| 120–139/80–89    | 964 (29.1)  | 814 (29.2)     | 150 (28.3) | |
| 140–159/90–99    | 1269 (38.3) | 1054 (37.9)    | 215 (40.6) | |
| ≥160/100         | 772 (23.3)  | 650 (23.3)     | 122 (23.0) | 0.563 |
| Uncontrolled high blood pressure (≥150/90 mm Hg), n (%) | 1481 (44.7) | 1236 (44.4) | 245 (46.2) | 0.433 |
| Orthostatic hypotension, n (%) | 721 (22.4) | 613 (24.9) | 108 (20.7) | 0.042 |
| Systolic blood pressure ≥160 mm Hg | 727 (21.9) | 613 (22.0) | 114 (21.5) | 0.798 |
| Diastolic blood pressure ≥100 mm Hg | 173 (5.2) | 140 (5.0) | 33 (6.2) | 0.256 |
| High cholesterol (>6.22 mmol/L), n (%) | 1523 (49.3) | 1228 (47.8) | 295 (56.4) | <0.01 |
| Diabetes mellitus, n (%) | 318 (10.2) | 277 (10.7) | 41 (7.8) | <0.05 |
| High CRP (>5 mg/L), n (%) | 626 (20.5) | 532 (21.1) | 94 (18.0) | <0.01 |
| Cardiovascular disease, n (%) | 1119 (33.3) | 976 (34.5) | 143 (27.0) | <0.01 |

Data are mean (SD), unless otherwise specified. CRP indicates C-reactive protein; MRI, magnetic resonance imaging.

*The number of participants with missing values was 32 in education, 102 in smoking, 97 in alcohol consumption, 329 in body mass index (1 person was in the MRI sample), 35 in hypertension, 48 in blood pressure, 384 in orthostatic hypotension (9 in the MRI sample), 48 in systolic pressure, 19 in diastolic pressure, 273 in total cholesterol (7 in the MRI sample), and 315 in CRP (8 in the MRI sample).
markers (eg, WMHs) in their analysis, even though MRI-visible PVSs and WMHs are closely correlated among older adults.3,6,28,29

In a clinical study of patients with ischemic stroke treated with intravenous thrombolysis, a high total load of SVD (WMHs, lacunes, and brain atrophy) was correlated with functional dependency and death at 90 days after stroke, but when individual SVD markers were analyzed separately, the association was evident only with severe WMHs, not with a large number of PVSs, lacunes, or atrophy.30 Another study found that 83% of the patients with hypertension had <10 PVSs in the basal ganglia region, among patients with SVD.31 Our observed associations of stage 2 hypertension with MRI-visible PVSs globally and of OH with higher PVS score in the basal ganglia region were diluted when adjusting for WMH load. These findings suggest that WMHs might be the main MRI marker for SVD in the basal ganglia region. Alternatively, it might suggest that WMHs and PVSs share a common origin, such as blood-brain barrier leakage,32 or even that enlarged PVSs might reflect a consequence of softening of the parenchyma attributable to WMHs.9,33,34

Our study revealed that the APOE ε4 allele might magnify the association of OH with lobar PVSs. Orthostatic hypotension gives rise to a decrease in flow velocity in the middle cerebral artery19 and a decrease in cerebral blood flow, at least in the frontal lobe.20 It has been suggested that brain hypoperfusion increases amyloid deposition,35 and because the clearance of metabolites such as amyloid through the PVS is dependent on arteriolar pulsations,36 this seems a reasonable assumption. It is also known that APOE ε4 carriers have an increased amount of amyloid in the brain.37,38 Amyloid deposition may in turn cause a widening of PVSs, as shown in patients with Alzheimer disease17 and cerebral amyloid angiopathy.39 Thus, our finding of an increased PVS number in persons with both OH and APOE ε4 allele (Figure) might imply that MRI-visible PVSs are a marker for amyloid-dependent SVD. This is supported by a positron emission tomography–computed tomography scan study, which suggests an association between cerebrovascular amyloid burden and MRI-visible PVSs in the centrum semiovale.40

Our study is based on a sample of relatively healthy older adults from the general population. Furthermore, the SNAC-K MRI database includes comprehensive data on demographics, lifestyle, health history, and health conditions. Thus, we could examine a range of vascular risk factors and control for major potential confounding factors. However, our study also has limitations. First, findings from a cross-sectional study are subject to selective survival bias, which may partly contribute to the negative associations between some vascular risk factors and PVS score. Furthermore, our study (sample size, n=530) might be underpowered to demonstrate a weak-to-moderate association between some vascular risk factors and MRI-visible PVSs. All these issues need to be kept in mind when interpreting our overall nonsignificant associations between vascular risk factors and MRI-visible PVS load.

**CONCLUSIONS**

We found limited evidence supporting a correlation of MRI-visible PVSs with vascular risk factors and the APOE ε4 allele. The potential associations of stage 2 hypertension (≥160/100 mm Hg) and OH with PVS scores were largely attributable to global WMH load. We detected an interaction of OH with the APOE ε4 allele for global and lobar PVS scores, which suggested a differential association of OH with lobar PVS score between carriers and noncarriers of the APOE ε4 allele. These findings suggest that
MRI-visible PVSs in the basal ganglia might not be a strong marker for hypertensive arteriopathy and other small-vessel lesions that are connected to vascular risk factors. However, PVSs in the lobar white matter might be a marker for cerebral amyloid angiopathy and other amyloid-dependent SVDs. Future population-based follow-up studies with large samples are warranted to further clarify the relationships of visible PVSs with vascular risk factors and genetic susceptibility (eg, APOE genotype).

**Table 3. β-Coefficient (95% CI) of Regional Perivascular Space Score With Vascular Risk Factors and APOE ε4 Allele**

| Vascular Risk Factors and APOE Genotype | β-Coefficient (95% CI), Lobar PVS Score | β-Coefficient (95% CI), Basal Ganglia PVS Score |
|-----------------------------------------|-----------------------------------------|-----------------------------------------------|
|                                        | Model 1*                                 | Model 2*                                      | Model 1*                                      | Model 2*                                      |
| Ever smoking                            | 0.05 (−0.53 to 0.63)                     | 0.08 (−0.52 to 0.68)                         | 0.09 (0.18 to 0.36)                           | −0.03 (−0.29 to 0.24)                        |
| Physical inactivity                     | −0.04 (−0.75 to 0.67)                    | 0.01 (−0.72 to 0.75)                         | 0.11 (−0.22 to 0.45)                         | 0.13 (−0.20 to 0.46)                        |
| Overweight or obesity (body mass index ≥25 kg/m²) | 0.14 (−0.43 to 0.71)                     | 0.16 (−0.43 to 0.74)                         | 0.07 (−0.20 to 0.34)                         | 0.10 (−0.17 to 0.36)                        |
| Hypertension                            | 0.18 (−0.50 to 0.87)                     | 0.17 (−0.53 to 0.88)                         | 0.14 (−0.19 to 0.46)                         | 0.04 (−0.28 to 0.35)                        |
| Blood pressure, mm Hg                   |                                         |                                              |                                              |                                              |
| <120/80                                 | 0.32 (−0.81 to 1.45)                     | 0.37 (−0.79 to 1.54)                         | −0.07 (−0.60 to 0.47)                        | 0.00 (−0.37 to 0.38)                        |
| 120–139/80–89                           | 0.00 (reference)                        | 0.00 (reference)                            | 0.00 (reference)                             | 0.00 (reference)                            |
| 140–159/90–99                           | 0.07 (−0.64 to 0.78)                     | 0.08 (−0.65 to 0.81)                         | 0.06 (−0.27 to 0.40)                         | 0.08 (−0.25 to 0.41)                        |
| ≥160/100                                | 0.56 (−0.25 to 1.36)                     | 0.55 (−0.29 to 1.39)                         | 0.14 (−0.24 to 0.53)                         | 0.02 (−0.50 to 0.54)                        |
| Uncontrolled high blood pressure (≥150/90 mm Hg) | 0.26 (−0.32 to 0.83)                     | 0.29 (−0.30 to 0.89)                         | 0.15 (−0.12 to 0.42)                         | 0.02 (−0.25 to 0.28)                        |
| Orthostatic hypotension                 | −0.02 (−0.72 to 0.69)                    | −0.13 (−0.87 to 0.61)                         | 0.37 (0.03 to 0.70)                          | 0.30 (−0.02 to 0.63)                        |
| Systolic blood pressure (≥160 mm Hg)    | 0.61 (−0.21 to 1.44)                     | 0.63 (−0.22 to 1.49)                         | 0.22 (−0.16 to 0.62)                         | 0.11 (−0.27 to 0.49)                        |
| Diastolic blood pressure (≥100 mm Hg)   | 1.30 (0.10 to 2.49)                      | 1.23 (−0.06 to 2.51)                         | 0.30 (−0.27 to 0.86)                         | 0.03 (−0.55 to 0.61)                        |
| High total cholesterol (≥6.22 mmol/L)   | 0.01 (−0.57 to 0.58)                     | 0.02 (−0.57 to 0.61)                         | −0.09 (−0.36 to 0.18)                        | −0.06 (−0.33 to 0.20)                       |
| Diabetes mellitus                       | −0.49 (−1.56 to 0.57)                    | −0.44 (−1.59 to 0.71)                        | −0.20 (−0.71 to 0.30)                        | −0.21 (−0.72 to 0.31)                       |
| High CRP (≥5 mg/L)                      | −0.18 (−0.90 to 0.56)                    | −0.12 (−0.89 to 0.65)                        | −0.18 (−0.53 to 0.18)                        | −0.07 (−0.41 to 0.28)                       |
| APOE ε4 allele                          | −0.25 (−0.90 to 0.40)                    | −0.32 (−0.99 to 0.36)                        | 0.11 (−0.20 to 0.42)                         | 0.03 (−0.28 to 0.33)                        |

CRP indicates C-reactive protein; and PVS, perivascular spaces.

*Model 1 was adjusted for age, sex, education, and cardiovascular disease, and model 2 was additionally adjusted for white matter hyperintensities.

†P<0.05.

**Figure 1. Association of orthostatic hypotension with global and regional MRI-visible perivascular spaces by APOE ε4 status.**

Model 1 was adjusted for age, sex, education, and cardiovascular disease; model 2 was additionally adjusted for white matter hyperintensities. *P<0.05. MRI indicates magnetic resonance imaging; and PVS, perivascular space.
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Disclosures

None.

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