Journal of the American Heart Association

ORIGINAL RESEARCH

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

Anna Laveskog, MD; Rui Wang, PhD; Davide L. Vetrano, MD, PhD; Lena Bronge, MD, PhD; Lars-Olof Wahlund, MD, PhD; Chengxuan Qiu, PhD

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.[1–6] In addition, a rather consistent association of enlarged PVSs with hypertension in older adults has been reported in several studies,[2,4,5,7,8] although some studies have shown no association with hypertension.[3,9,10] 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.[11] 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.[3,6] 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

Correspondence to: Anna Laveskog, MD, Department of Neuroradiology, Karolinska University Hospital, S-171 76 Stockholm, Sweden. E-mail: anna.laveskog@sll.se, or Chengxuan Qiu, PhD, Aging Research Center, Karolinska Institutet, Tomtebodavägen 18A, S-171 65 Solna, Sweden. E-mail: chengxuan.qiu@ki.se

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- We found limited evidence for a correlation of magnetic resonance imaging–visible perivascular spaces (PVSs) with vascular risk factors in older adults, but the association of lobar PVSs with orthostatic hypotension among *APOE* ε4 carriers suggests that lobar PVSs may be a marker for amyloid-related cerebral 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

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

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.[5,12] Indeed, neuroimaging studies have suggested that different SVD markers are associated with different risk factors, depending on their location.[12,13]

Evidence has emerged that cerebral SVD markers, such as WMHs and MRI-visible PVSs, are highly heritable and that the heritability may vary by different brain regions.[14,15] Some studies suggest that PVSs are more common in *APOE* ε4 allele carriers,[16,17] while others show no association with the APOE ε4 allele.[1,5] However, population-based studies that explore the potential interaction of vascular risk factors and genetic susceptibility with enlarged PVSs are still lacking.

In a study of healthy adult volunteers, the supine-to-standing postural change was associated with a decreasing fraction of oxygenated hemoglobin in the frontal lobes,[18] as well as a lower blood flow velocity in the middle cerebral artery.[19] In addition, studies of patients with orthostatic hypotension (OH) have shown that cerebral blood flow and oxygenated hemoglobin in the frontal lobes tend to decrease even more with orthostatic stress, and the blood flow velocity in the middle cerebral artery decreased significantly more than in healthy controls.[19,20] This might explain the finding in a large population-based study of older adults (the Three-City Study) that OH at baseline was associated with an increased risk of incident dementia during a 12-year follow-up period.[21]

The overall aim of this population-based study of Swedish older adults is to examine the association of MRI-visible PVSs with vascular risk factors and *APOE* genotype and, further, to explore whether different vascular risk factors and *APOE* ε4 allele have interactive effects on visible PVSs. We hypothesize that PVSs, as a marker of cerebral SVD, may be correlated with vascular risk factors and the *APOE* ε4 allele in old age.

METHODS

Data for this study were derived from the data set of the SNAC-K (Swedish National Study on Aging and Care in Kungsholmen) population study. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols for purposes of reproducing the results or replicating the procedure may be sent to the data manager for the SNAC-K population study. More information about data availability and application form, can be found at www.snac-k.se/for-researchers/application-form/.

Study Participants

Participants were derived from the population-based SNAC-K, a multidisciplinary study of aging and care, as fully reported elsewhere.[22–24] Briefly, at baseline the SNAC-K sample included 4 younger cohorts with a 6-year age interval (60, 66, 72, and 78 years) and 7 older cohorts with a 3-year age interval (81, 84, 87, 90, 93, 96, and 99+ years). Of all 4590 persons who were eligible to participate, 3363 (73.3%) were examined at baseline (March 2001–June 2004). During September 2001 to October 2003, 555 noninstitutionalized, nondisabled, and nondemented participants also underwent brain MRI examinations. Of these, 2 people did not complete the entire MRI examination because of claustrophobia, 4 had suboptimal MRIs because of motion artifacts, 2 were excluded because of large meningiomas, and MRIs were lost for 17 people because of technical problems. Therefore, 530 participants were

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.[6,25] 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 A_{1c} >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 (I48). *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 heteroskedasticity) 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

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

Characteristics*	Total Sample (n=3363)	Brain MRI data		
		No (n=2833)	Yes (n=530)	*P* Value
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)	67 (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 (%)	1163 (35.6)	1052 (37.1)	111 (20.9)	<0.01
Body mass index (kg/m^2), n (%)				
Normal (<25)	1448 (47.7)	1216 (48.5)	232 (43.9)	
Overweight (25–29.9)	1198 (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 (24.2)	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).

(≥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 noncarriers 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,[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,[2,4,5,7,8] smoking,[12] diabetes mellitus,[26] and inflammatory markers.[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.[3,9,10] In addition, most of the previous studies have not examined the effect of other SVD

Table 2. β-Coefficient (95% CI) of Global Perivascular Space Score With Vascular Risk Factors and *APOE* ε4 Allele

Vascular Risk Factors and *APOE* Genotype	β-Coefficient (95% CI), Global Perivascular Space Score	
	Model 1*	Model 2*
Ever smoking	0.25 (−0.64 to 1.13)	0.08 (−0.83 to 0.98)
Physical inactivity	0.35 (−0.73 to 1.44)	0.36 (−0.75 to 1.47)
Overweight or obesity (body mass index ≥25 kg/m^2)	0.30 (−0.57 to 1.16)	0.40 (−0.48 to 1.28)
Hypertension	0.74 (−0.29 to 1.77)	0.51 (−0.54 to 1.56)
Blood pressure, mm Hg		
<120/80	0.57 (−2.29 to 1.15)	0.47 (−2.21 to 1.27)
120 to 139/80 to 89	0.00 (reference)	0.00 (reference)
140 to 159/90 to 99	0.50 (−0.58 to 1.59)	0.44 (−0.66 to 1.54)
≥160/100	1.30 (0.06 to 2.53)†	1.03 (−0.24 to 2.30)
Uncontrolled high blood pressure (≥150/90 mm Hg)	0.79 (−0.09 to 1.67)	0.57 (−0.33 to 1.47)
Orthostatic hypotension	0.47 (−0.62 to 1.55)	0.21 (−0.90 to 1.33)
Systolic blood pressure ≥160 mm Hg	1.46 (0.20 to 2.72)†	1.29 (0.01 to 2.58)†
Diastolic blood pressure ≥100 mm Hg	2.33 (0.49 to 4.16)†	1.80 (−0.14 to 3.75)
High total cholesterol (≥6.22 mmol/L)	0.20 (−0.67 to 1.07)	0.29 (−0.59 to 1.18)
Diabetes mellitus	−1.32 (−2.96 to 0.31)	−1.37 (−3.10 to 0.35)
APOE ε4 allele	−0.33 (−1.34 to 0.67)	−0.52 (−1.54 to 0.49)
High CRP (>5 mg/L)	−0.92 (−2.06 to 0.21)	−0.76 (−1.91 to 0.39)

CRP indicates C-reactive protein.
*Model 1 was adjusted for age, sex, education, and cardiovascular disease, and model 2 was additionally adjusted for white matter hyperintensities.
†$P<0.05$.

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 artery[19] 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 disease[17] 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

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/m^2)	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 (−0.93 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.

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).

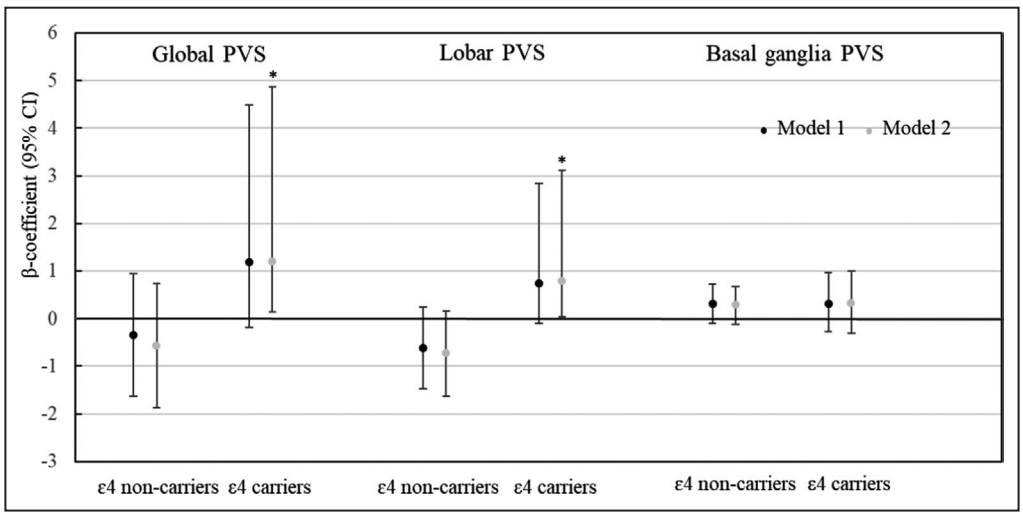

Figure 1. Association of orthostatic hypotension with global and regional MRI-visible perivascular spaces by APOE ε4 status.
Model 1 was adjusted for age, sex, education, and cardiovascular disease; model 2 was additionally adjusted for white matter hyperintensities. *P<0.05. MRI indicates magnetic resonance imaging; and PVS, perivascular space.

ARTICLE INFORMATION

Received January 17, 2020; accepted July 14, 2020.

Affiliations

From the Division of Neuro, Department of Clinical Neuroscience, Karolinska Institutet (A.L., L.B.), Department of Neuroradiology, Karolinska University Hospital, Stockholm, Sweden (A.L.); Department of Neurobiology, Care Sciences and Society (NVS), Aging Research Center, Karolinska Institutet-Stockholm University, Stockholm, Sweden (R.W., D.L.V., C.Q.); Centro di Medicina dell'Invecchiamento, IRCCS Fondazione Policlinico "A. Gemelli" Catholic University of Rome, Italy (D.L.V.); and Division of Clinical Geriatrics, NVS, Karolinska Institutet, Stockholm, Sweden (L.-O.W.).

Acknowledgments

The authors thank all the SNAC-K MRI participants for their contributions to the project and our colleagues in the SNAC-K group for their work in data collection and management. The manuscript was edited by Dr Heather Martin from the Department of Neuroradiology, Karolinska University Hospital, Stockholm, Sweden.

Sources of Funding

SNAC-K was supported by the Swedish Ministry of Health and Social Affairs, the Stockholm County Council, Stockholm Municipality, and the Swedish Research Council. This work was further supported in part by grants from the Swedish Research Council (VR, grants no.: 2015-02531, 2016-06658, 2017-05819, and 2017-00740), the Swedish Research Council for Health, Working Life and Welfare (FORTE, grant no.: 2014-01382), the Swedish Foundation for International Cooperation in Research and Higher Education (STINT, grant no.: CH2019-8320), and Karolinska Institutet, Stockholm, Sweden.

Disclosures

None.

REFERENCES

1. Zhu YC, Tzourio C, Soumare A, Mazoyer B, Dufouil C, Chabriat H. Severity of dilated Virchow-Robin spaces is associated with age, blood pressure, and MRI markers of small vessel disease: a population-based study. *Stroke*. 2010;41:2483–2490.
2. Gutierrez J, Rundek T, Ekind MSV, Sacco RL, Wright CB. Perivascular spaces are associated with atherosclerosis: an insight from the Northern Manhattan study. *AJNR Am J Neuroradiol*. 2013;34:1711–1716.
3. Potter GM, Doubal FN, Jackson CA, Chappell FM, Sudlow CL, Dennis MS, Wardlaw JM. Enlarged perivascular spaces and cerebral small vessel disease. *Int J Stroke*. 2015;10:376–381.
4. Lau KK, Li L, Lovelock CE, Zamboni G, Chan TT, Chiang MF, Lo KT, Küker W, Mak HK, Rothwell PM. Clinical correlates, ethnic differences, and prognostic implications of perivascular spaces in transient ischemic attack and ischemic stroke. *Stroke*. 2017;48:1470–1477.
5. Shams S, Martola J, Charidimou A, Larvie M, Granberg T, Shams M, Kristoffersen-Wiberg M, Wahlund LO. Topography and determinants of magnetic resonance imaging (MRI)-visible perivascular spaces in a large memory clinic cohort. *J Am Heart Assoc*. 2017;6:e006279. DOI: 10.1161/JAHA.117.006279.
6. Laveskog A, Wang R, Bronge L, Wahlund LO, Qiu C. Perivascular spaces in old age: assessment, distribution, and correlation with white matter hyperintensities. *AJNR Am J Neuroradiol*. 2018;39:70–76.
7. Hiroki M, Miyashita K. Linear hyperintensity objects on magnetic resonance imaging related to hypertension. *Cerebrovasc Dis*. 2001;11:164–168.
8. Martinez-Ramirez S, Pontes-Neto OM, Dumas AP, Auriel E, Halpin A, Quimby M, Gurol ME, Greenberg SM, Viswanathan A. Topography of dilated perivascular spaces in subjects from a memory clinic cohort. *Neurology*. 2013;80:1551–1556.
9. Sahin N, Solak A, Genc B, Akpinar MB. Dilatation of the Virchow-Robin spaces as an indicator of unilateral carotid artery stenosis: correlation with white matter lesions. *Acta Radiol*. 2015;56:852–859.
10. Bouvy WH, Zwanenburg JJ, Reinink R, Wisse LE, Luijten PR, Kappelle LJ, Geerlings MI, , Biessels GJ; Utrecht Vascular Cognitive Impairment (VCI) Study Group. Perivascular spaces on 7 Tesla brain MRI are related to markers of small vessel disease but not to age or cardiovascular risk factors. *J Cereb Blood Flow Metab*. 2016;36:1708–1717.
11. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol*. 2010;9:689–701.
12. Yakushiji Y, Charidimou A, Hara M, Noguchi T, Nishihara M, Eriguchi M, Nanri Y, Nishiyama M, Werring DJ, Hara H. Topography and associations of perivascular spaces in healthy adults: the Kashima Scan Study. *Neurology*. 2014;83:2116–2123.
13. Yang H, Shen R, Jin Z, Li J, Wu Y, Xu Y, Hua T, Liu X, Huang J. Dilated Virchow-Robin spaces in first-ever lacunar stroke patients: topography and clinical correlations. *J Stroke Cerebrovasc Dis*. 2016;25:306–311.
14. Sachdev PS, Thalamuthu A, Mather KA, Ames D, Wright MJ, Wen W. White matter hyperintensities are under strong genetic influence. *Stroke*. 2016;47:1422–1428.
15. Duperron MG, Tzourio C, Sargurupremraj M, Mazoyer B, Soumaré A, Schilling S, Amouyel P, Chauhan G, Zhu YC, Debette S. Burden of dilated perivascular spaces, an emerging marker of cerebral small vessel disease, is highly heritable. *Stroke*. 2018;49:282–287.
16. Barboriak DP, Doraiswamy PM, Krishnan KR, Vidyarthi S, Sylvester J, Charles HC. Hippocampal sulcal cavities on MRI: relationship to age and apolipoprotein E genotype. *Neurology*. 2000;54:2150–2153.
17. Roher AE, Kuo YM, Esh C, Knebel C, Weiss N, Kalback W, Luehrs DC, Childress JL, Beach TG, Weller RO, et al. Cortical and leptomeningeal cerebrovascular amyloid and white matter pathology in Alzheimer's disease. *Mol Med*. 2003;9:112–122.
18. Edlow BL, Kim MN, Durduran T, Zhou C, Putt ME, Yodh AG, Greenberg JH, Detre JA. The effects of healthy aging on cerebral hemodynamic responses to posture change. *Physiol Meas*. 2010;31:477–495.
19. Krakow K, Ries S, Daffertshofer M, Hennerici MG. Simultaneous assessment of brain tissue oxygenation and cerebral perfusion during orthostatic stress. *Eur Neurol*. 2000;43:39–46.
20. Passant U, Warkentin S, Minthon L, Fäldt R, Edvinsson L. Cortical blood flow during head-up postural change in subjects with orthostatic hypotension. *Clin Auton Res*. 1993;3:311–318.
21. Cremer A, Soumaré A, Berr C, Dartigues JF, Gabelle A, Gosse P, Tzourio C. Orthostatic hypotension and risk of incident dementia: results from a 12-year follow-up of the Three-City study cohort. *Hypertension*. 2017;70:44–49.
22. Lagergren M, Fratiglioni L, Hallberg IR, Berglund J, Elmstahl S, Hagberg B, Holst G, Rennemark M, Sjölund BM, Thorslund M, et al. A longitudinal study integrating population, care and social services data. The Swedish National study on Aging and Care (SNAC). *Aging Clin Exp Res*. 2004;16:158–168.
23. Wang R, Fratiglioni L, Laveskog A, Kalpouzos G, Ehrenkrona CH, Zhang Y, Bronge L, Wahlund LO, Bäckman L, Qiu C. Do cardiovascular risk factors explain the link between white matter hyperintensities and brain volumes in old age? A population-based study. *Eur J Neurol*. 2014;21:1076–1082.
24. Welmer A-K, Rizzuto D, Qiu C, Caracciolo B, Laukka EJ. Walking speed, processing speed, and dementia: a population-based longitudinal study. *J Gerontol A Biol Sci Med Sci*. 2014;69:1503–1510.
25. Scheltens P, Barkhof F, Leys D, Pruvo JP, Nauta JJ, Vermersch P, Steinling M, Valk J. A semiquantative rating scale for the assessment of signal hyperintensities on magnetic resonance imaging. *J Neurol Sci*. 1993;114:7–12.
26. Rouhl RP, van Oostenbrugge RJ, Knottnerus IL, Staals JE, Lodder J. Virchow-Robin spaces relate to cerebral small vessel disease severity. *J Neurol*. 2008;255:692–696.
27. Satizabal CL, Zhu YC, Dufouil C, Tzourio C. Inflammatory proteins and the severity of dilated Virchow-Robin spaces in the elderly. *J Alzheimers Dis*. 2013;33:323–328.
28. Aribisala BS, Wiseman S, Morris Z, Valdés-Hernández MC, Royle NA, Maniega SM, Gow AJ, Corley J, Bastin ME, Starr J, et al. Circulating inflammatory markers are associated with magnetic resonance imaging-visible perivascular spaces but not directly with white matter hyperintensities. *Stroke*. 2014;45:605–607.
29. Doubal FN, MacLullich AM, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease. *Stroke*. 2010;41:450–454.
30. Arba F, Inzitari D, Ali M, Warach SJ, Luby M, Lees KR. Small vessel disease and clinical outcomes after IV rt-PA treatment. *Acta Neurol Scand*. 2017;136:72–77.

31. Huijts M, Duits A, Staals J, Kroon AA, de Leeuw PW, van Oostenbrugge RJ. Basal ganglia enlarged perivascular spaces are linked to cognitive function in patients with cerebral small vessel disease. *Curr Neurovasc Res*. 2014;11:136–141.
32. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *Lancet Neurol*. 2013;12:483–497.
33. Kirkpatrick JB, Hayman LA. White-matter lesions in MR imaging of clinically healthy brains of elderly subjects: possible pathologic basis. *Radiology*. 1987;162:509–511.
34. Brown WR, Moody DM, Challa VR, Thore CR, Anstrom JA. Venous collagenosis and arteriolar tortuosity in leukoaraiosis. *J Neurol Sci*. 2002;203-204:159–163.
35. Okamoto Y, Yamamoto T, Kalaria RN, Senzaki H, Maki T, Hase Y, Kitamura A, Washida K, Yamada M, Ito H, et al. Cerebral hypoperfusion accelerates cerebral amyloid angiopathy and promotes cortical microinfarcts. *Acta Neuropathol*. 2012;123:381–394.
36. Esiri MM, Gay D. Immunological and neuropathological significance of the Virchow-Robin space. *J Neurol Sci*. 1990;100:3–8.
37. Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, Pericak-Vance MA, Goldgaber D, Roses AD. Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. *Proc Natl Acad Sci U S A*. 1993;90:9649–9653.
38. Greenberg SM, Rebeck GW, Vonsattel JP, Gomez-Isla T, Hyman BT. Apolipoprotein E ε4 and cerebral hemorrhage associated with amyloid angiopathy. *Ann Neurol*. 1995;38:254–259.
39. van Veluw SJ, Biessels GJ, Bouvy WH, Spliet WG, Zwanenburg JJ, Luijten PR, Macklin EA, Rozemuller AJ, Gurol ME, Greenberg SM, et al. Cerebral amyloid angiopathy severity is linked to dilation of juxtacortical perivascular spaces. *J Cereb Blood Flow Metab*. 2016;36:576–580.
40. Charidimou A, Hong YT, Jäger HR, Fox Z, Aigbirhio FI, Fryer TD, Menon DK, Warburton EA, Werring DJ, Baron JC. White matter perivascular spaces on magnetic resonance imaging: marker of cerebrovascular amyloid burden? *Stroke*. 2015;46:1707–1709.