WITH advancing age, an increased visibility of perivascular spaces (PVSs) on magnetic resonance imaging (MRI) is hypothesized to represent impaired drainage of interstitial fluid from the brain and may reflect underlying cerebral small vessel disease (SVD). However, whether large perivascular spaces (L-PVSs) (>3 mm in diameter) visible on MRI are associated with SVD and cognitive deterioration in older individuals is unknown.

OBJECTIVE To examine whether L-PVSs are associated with the progression of the established MRI markers of SVD, cognitive decline, and increased risk of dementia.

DESIGN, SETTING, AND PARTICIPANTS The prospective, population-based Age, Gene/Environment Susceptibility–Reykjavik Study assessed L-PVS at baseline (September 1, 2002, through February 28, 2006) on MRI studies of the brain in 2612 participants. Participants returned for additional MRI from April 1, 2007, through September 30, 2011, and underwent neuropsychological testing at the 2 time points a mean (SD) of 5.2 (0.2) years apart. Data analysis was conducted from August 1, 2016, to May 4, 2017.

EXPOSURES The presence, number, and location of L-PVSs.

MAIN OUTCOMES AND MEASURES Incident subcortical infarcts, cerebral microbleeds, and progression of white matter hyperintensities detected on MRI; cognitive decline defined as composite score changes between baseline and follow-up in the domains of memory, information processing speed, and executive function; and adjudicated incident dementia cases diagnosed according to international guidelines.

RESULTS Of the 2612 study patients (mean [SD] age, 74.6 [4.8] years; 1542 [59.0%] female), 424 had L-PVSs and 2188 did not. The prevalence of L-PVSs was 16.2% (median number of L-PVSs, 1; range, 1-17). After adjusting for age, sex, and interval between baseline and follow-up scanning, the presence of L-PVSs was significantly associated with an increased risk of incident subcortical infarcts (adjusted risk ratio, 2.54; 95% CI, 1.76-3.68) and microbleeds (adjusted risk ratio, 1.43; 95% CI, 1.18-1.72) and a greater 5-year progression of white matter hyperintensity volume. The presence of L-PVSs was also associated with a steeper decline in information processing speed and more than quadrupled the risk of vascular dementia. All associations persisted when further adjusted for genetic and cerebrovascular risk factors. The associations with cognitive outcomes were independent of educational level, depression, and other SVD MRI markers.

CONCLUSIONS AND RELEVANCE Large PVSs are an MRI marker of SVD and associated with the pathogenesis of vascular-related cognitive impairment in older individuals. Large PVSs should be included in assessments of vascular cognitive impairment in the older population and as potential targets for interventions.

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Cerebral small vessel disease (SVD) is a major contributor to cognitive impairment in older individuals.\(^1\,\,^2\) In addition to well-established neuroimaging hallmarks of SVD, including small subcortical infarcts, white matter hyperintensities (WMHs), and microbleeds, magnetic resonance imaging (MRI)-visible perivascular spaces (PVSs) are emerging as a potential SVD marker. The PVSs are fluid-filled cavities that surround small, penetrating cerebral arterioles and venules and are commonly considered to play an important role in forming a network of drainage channels for the elimination of metabolic waste and fluid from the brain.\(^3\) When the caliber and the number of normally microscopic PVSs increases with advancing age, PVSs appear on T2-weighted MRI as round or tubular hyperintensities in the basal ganglia and white matter.\(^4\,\,^6\) With regard to pathologic features, the mechanisms underlying the PVSs may involve the 2 most common sporadic forms of SVD, which are hypertensive arteriopathy and cerebral amyloid angiopathy (CAA), plausibly leading to different anatomical PVS patterns.\(^1\,\,^7\)

There is increasing epidemiologic evidence that PVSs are associated with some MRI manifestations of SVD and cognitive impairment in patients with cerebrovascular disease\(^8\,\,^9\,\,^10\) or dementia\(^11\,\,^12\) and in neurologically healthy adults.\(^7\,\,^13\,\,^14\) To date, longitudinal data are scarce,\(^15\) and the clinical significance of PVSs in the general population of older individuals remains uncertain. Looking prospectively at the association would help to disentangle the complex interplay between PVSs and other SVDs and better define the cognitive consequence of PVSs.

Previous studies\(^7\,\,^10\,\,^16\) focused on detecting smaller PVS lesions with a maximum diameter less than 3 mm on MRI in an attempt to separate PVSs from lacunes of presumed vascular origin, although pathologic studies\(^17\,\,^18\) have not found an absolute cutoff size to discriminate between the 2 lesions. We examined large PVSs (L-PVSs) with diameters greater than 3 mm, which are morphologically distinguished from lacunes on MRI. Large PVSs are frequently encountered in ostensibly healthy older individuals, and their prevalence increases with higher numbers of smaller PVSs.\(^19\) We thus investigated in a large, well-characterized cohort of older individuals the prospective associations between prevalent L-PVSs and progression of the MRI markers of SVD, cognitive decline, and risk of new-onset dementia.

Methods

Participants

This investigation was conducted as part of the prospective, population-based Age, Gene/Environment Susceptibility-Reykjavik (AGES-Reykjavik) Study, which originates from the Reykjavik Study, as described in detail previously.\(^20\) In brief, from September 1, 2002, through February 28, 2006, a total of 5764 surviving men and women of the Reykjavik Study cohort born from 1907 to 1935 underwent extensive physical, cognitive, and brain MRI examinations (AGES I). From April 1, 2007, through September 30, 2011, follow-up examination was performed of all surviving patients who agreed to participate (AGES II). Participants who returned for follow-up underwent neuropsychological testing at the 2 time points a mean (SD) of 5.2 (0.2) years apart. Of the 3316 participants who attended the follow-up examination, we excluded 654 participants if the baseline MRIs were unavailable, incomplete, or of inadequate quality. In total, 2612 participants without prevalent dementia were included in the SVD progression analysis. Of these, 2592 participants were included in the dementia analysis and 2551 participants were included in the cognitive decline analysis (eMethods, eFigure 1, and eTable 1 in the Supplement). All participants gave written informed consent, and all data were deidentified. The study was approved by the Icelandic National Bioethics Committee and the National Institute on Aging Intramural Institutional Review Board.

Brain MRI and L-PVS Assessment

We performed brain MRI on a study-dedicated 1.5-T scanner (Signa Twinspeed; General Electric Medical Systems). The same MRI protocol, described elsewhere,\(^21\,\,^22\) was used at baseline and follow-up and included the following pulse sequences\(^21\): 3-dimensional, T1-weighted, spoiled-gradient echo sequence; proton density/T2-weighted fast spin echo sequence; fluid attenuated inversion recovery (FLAIR) sequence, and T2*-weighted gradient-echo-type echo planar (eMethods in the Supplement). The volume of WMH was quantified automatically and expressed as the percentage of total intracranial volume.\(^22\) Microbleeds were defined as a focal area of signal void in the brain parenchyma that was visible on T2*-weighted gradient-echo-type echo planar and smaller or invisible on T2-weighted fast spin-echo scans.\(^21\,\,^23\,\,^24\) Subcortical infarcts were defined as brain parenchymal defects with a minimum diameter of 4 mm not extending into the cortex, with a signal intensity equal to cerebrospinal fluid on all pulse sequences and surrounded by an area of high signal intensity on FLAIR images.\(^25\)

To distinguish PVSs from subcortical infarcts, L-PVSs were evaluated separately and defined as round or tubular defects with a short axis larger than 3 mm in the subcortical area, without a rim or area of high signal intensity on the axial FLAIR...
(characteristics for infarcts) and without evidence of hemosiderin in its wall on the axial T2*-weighted gradient-echo type echo planar (characteristics for resorbed hemorrhagic lesions) (Figure). The total L-PVS number was based on the presence in the basal ganglia complex (caudate nucleus, internal capsule, external capsule, thalamus, and lentiform nucleus [putamen and globus pallidus]) along the paths of the perforating lenticulostriate arteries (arising from the middle cerebral artery) and in white matter along the paths of the perforating medullary arteries. Intrarater reliability values (κ) for L-PVSs based on 2 ratings within a 6-month interval were 0.88 and 0.93, and the interrater agreement value was 0.66, indicating good reliability. Our scan protocol could not be designed to capture smaller PVSs (ie, ≤3 mm in diameter) because the section thickness of the 2-dimensional FLAIR, proton density, and T2-weighted scans was 3 mm, and the nature of smaller lesions was more difficult to assess reliably.

The presence of L-PVSs, microbleeds, and subcortical infarcts on the baseline and follow-up scans was assessed by trained radiographers. They were initially masked to the baseline MRI and identified new lesions on the follow-up MRI. If a lesion was detected on the follow-up MRI, the baseline MRI was examined to determine whether the lesion was present in the same section location. If so, the follow-up lesion was labeled prevalent; if not, the lesion was labeled incident.

Assessment of Cognitive Function
Participants underwent a neuropsychological test battery that assessed 3 cognitive domains25: verbal memory, processing speed, and executive function (eMethods in the Supplement). The composite score for each cognitive domain was calculated by converting raw scores to standardized z scores and averaging them across all tests for the domain.25 For each participant, we computed z scores for baseline and follow-up using the mean (SD) of the baseline test scores. Cognitive decline was calculated by subtracting the baseline domain-specific z scores from the follow-up z scores.

Dementia Diagnosis
Incident dementia cases were identified at follow-up examination based on a 3-step procedure, and the diagnosis of dementia and subtypes was assigned at a consensus conference (eMethods in the Supplement).25 Vascular dementia (VaD) was diagnosed in accordance with the criteria of the State of California Alzheimer Disease Diagnostic and Treatment Centers.26,27

Statistical Analysis
Large PVSs were further categorized into a trichotomous variable (none, 1, and ≥2). Because the anatomical distribution of L-PVSs may reflect different SVD types, we also examined L-PVSs by location: a white matter distribution exclusively and those in the basal ganglia with and without concomitant white matter L-PVSs.

We constructed multiple logistic regression models and performed the postestimations (Stata adjrr command) to calculate the adjusted risk ratios (aRRs; ie, the ratio of the mean predicted probabilities between those with and without the L-PVSs) and 95% CIs for the associations between L-PVS presence and...
incident subcortical infarcts, microbleeds, and dementia. We estimated the association between L-PVS presence and subsequent WMH progression and cognitive decline by multiple linear regression analyses. The changes scores for WMH volume and processing speed were logarithmically transformed to normalize their skewed distributions. All analyses were initially adjusted for age, sex, and interval between the baseline and follow-up MRIs (model 1), followed by additional adjustment for head coil, body mass index, current smoking, hypertension, total cholesterol level, prevalent symptomatic stroke, and APOE4 genotype (model 2). With respect to the association with cognitive outcomes, we adjusted for educational level, depression, baseline cerebral infarcts, microbleeds, and WMHs in addition to the aforementioned variables (except for stroke) in model 2. Interactions between L-PVSs and other covariates with respect to effects on SVD and cognitive outcomes were assessed in the fully adjusted models by including cross-product terms of each covariate with L-PVSs. All analyses were repeated for the number and location of L-PVSs, and the association with L-PVS location was examined while controlling for L-PVSs at other locations. Because the occurrence of dementia events was low \( n < 5 \) in L-PVS number or location categories, we applied the Fisher exact test to examine the crude associations between L-PVS number or location and dementia. To test the robustness of the results, we performed several sensitivity analyses (eMethods, eResults, and eTables 2 and 3 in the Supplement). We used 2-tailed \( t \) tests and Wald tests as appropriate, and a 2-sided \( P < .05 \) was taken to indicate statistical significance.

### Results

Of the 2612 study patients (mean [SD] age, 74.6 [4.8] years; 1542 [59.0%] female), 2188 (83.8%) did not have L-PVSs and 424 (16.2%) had L-PVSs (median number of L-PVSs, 1; range, 1-17; 1-L-PVS, 315 [12.1%]; \( \geq 2 \) L-PVSs, 109 [4.2%]) (Table I). Among participants with L-PVSs, 75 (17.7%) had white matter L-PVSs exclusively and 349 (82.3%) had basal ganglia L-PVSs with and without concomitant white matter L-PVSs (including those with

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Population (N = 2612)</th>
<th>L-PVSs Absent (n = 2188)</th>
<th>L-PVSs Present (n = 424)</th>
<th>( P ) Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>74.6 (4.8)</td>
<td>74.5 (4.8)</td>
<td>75.2 (4.7)</td>
<td>.005</td>
</tr>
<tr>
<td>Women</td>
<td>1542 (59.0)</td>
<td>1311 (59.9)</td>
<td>231 (54.5)</td>
<td>.04</td>
</tr>
<tr>
<td>Primary education only</td>
<td>522 (20.1)</td>
<td>439 (20.2)</td>
<td>83 (19.6)</td>
<td>.56</td>
</tr>
<tr>
<td>MMSE score, median (IQR)</td>
<td>28.0 (26.0-29.0)</td>
<td>28.0 (26.0-29.0)</td>
<td>28.0 (26.0-29.0)</td>
<td>.47</td>
</tr>
<tr>
<td>Depressive symptoms at baseline</td>
<td>120 (4.8)</td>
<td>96 (4.6)</td>
<td>24 (5.9)</td>
<td>.23</td>
</tr>
<tr>
<td>Depressive symptoms at follow-up</td>
<td>166 (6.5)</td>
<td>130 (6.0)</td>
<td>36 (8.6)</td>
<td>.07</td>
</tr>
<tr>
<td>APOE4 allele carriers</td>
<td>681 (26.1)</td>
<td>561 (25.7)</td>
<td>120 (28.3)</td>
<td>.19</td>
</tr>
</tbody>
</table>

**Cardiovascular risk factors or disease**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Population (N = 2612)</th>
<th>L-PVSs Absent (n = 2188)</th>
<th>L-PVSs Present (n = 424)</th>
<th>( P ) Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index, mean (SD)(^c)</td>
<td>27.2 (4.1)</td>
<td>27.4 (4.2)</td>
<td>26.7 (3.9)</td>
<td>.003</td>
</tr>
<tr>
<td>Current smoker</td>
<td>276 (10.6)</td>
<td>221 (10.1)</td>
<td>55 (13.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Systolic blood pressure, mean (SD), mm Hg</td>
<td>141.1 (19.7)</td>
<td>140.8 (19.8)</td>
<td>142.7 (19.1)</td>
<td>.15</td>
</tr>
<tr>
<td>Diastolic blood pressure, mean (SD), mm Hg</td>
<td>74.2 (9.3)</td>
<td>74.0 (9.2)</td>
<td>74.9 (9.6)</td>
<td>.04</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2027 (77.6)</td>
<td>1696 (77.5)</td>
<td>331 (78.1)</td>
<td>.88</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>243 (9.3)</td>
<td>198 (9.1)</td>
<td>45 (10.6)</td>
<td>.28</td>
</tr>
<tr>
<td>Total cholesterol, mean (SD), mg/dL</td>
<td>220 (42)</td>
<td>220 (42)</td>
<td>216 (46)</td>
<td>.046</td>
</tr>
<tr>
<td>History of symptomatic stroke</td>
<td>77 (3.0)</td>
<td>60 (2.7)</td>
<td>17 (4.0)</td>
<td>.19</td>
</tr>
</tbody>
</table>

**Medication use**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Population (N = 2612)</th>
<th>L-PVSs Absent (n = 2188)</th>
<th>L-PVSs Present (n = 424)</th>
<th>( P ) Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of blood pressure–lowering medication</td>
<td>1573 (60.2)</td>
<td>1307 (59.7)</td>
<td>266 (62.7)</td>
<td>.37</td>
</tr>
<tr>
<td>Statin</td>
<td>623 (23.9)</td>
<td>512 (23.4)</td>
<td>111 (26.2)</td>
<td>.23</td>
</tr>
</tbody>
</table>

**Brain MRI markers**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Population (N = 2612)</th>
<th>L-PVSs Absent (n = 2188)</th>
<th>L-PVSs Present (n = 424)</th>
<th>( P ) Value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral infarcts</td>
<td>803 (30.7)</td>
<td>630 (28.8)</td>
<td>173 (40.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Subcortical infarcts</td>
<td>192 (7.4)</td>
<td>132 (6.0)</td>
<td>60 (14.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Microbleeds</td>
<td>445 (17.0)</td>
<td>362 (16.5)</td>
<td>83 (19.6)</td>
<td>.19</td>
</tr>
<tr>
<td>White matter hyperintensity volume, median (IQR), mL</td>
<td>11.6 (6.5-21.5)</td>
<td>11.1 (6.4-20.1)</td>
<td>15.2 (8.1-27.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; L-PVSs, large perivascular spaces; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging.

\(^{a}\) Conversion factor: to convert total cholesterol to millimoles per liter, multiply by 0.0259.

\(^{b}\) Age adjusted.

\(^{c}\) Calculated as weight in kilograms divided by height in meters squared.

Table I. Characteristics of the Study Population According to the Presence of L-PVSs Visible on MRI in the Age, Gene/Environment Susceptibility I Study\(^a\)

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Table 2. Association of Prevalent L-PVSs Vi on MRI With Progression of Cerebral Small Vessel Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Incident Subcortical Infarcts</th>
<th>Incident Cerebral Microbleeds</th>
<th>WMH Volume Progression, β (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of Patients Model 1b Model 2c</td>
<td>No of Patients Model 1b Model 2c</td>
<td>No of Patients Model 1b Model 2c</td>
</tr>
<tr>
<td>Baseline presence of L-PVSs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 424)</td>
<td>40 2.54 (1.76 to 3.68) 2.42 (1.67 to 3.51)</td>
<td>107 1.43 (1.18 to 1.72) 1.39 (1.15 to 1.67)</td>
<td>0.04 (0.01 to 0.06) 0.03 (0.01 to 0.05)</td>
</tr>
<tr>
<td>Baseline L-PVS number</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (n = 315)</td>
<td>28 2.43 (1.62 to 3.65) 2.34 (1.56 to 3.52)</td>
<td>75 1.35 (1.08 to 1.67) 1.31 (1.06 to 1.63)</td>
<td>0.03 (0.003 to 0.06) 0.02 (-0.00 to 0.05)</td>
</tr>
<tr>
<td>≥2 (n = 109)</td>
<td>12 2.70 (1.54 to 4.74) 2.51 (1.42 to 4.43)</td>
<td>32 1.64 (1.21 to 2.22) 1.58 (1.17 to 2.15)</td>
<td>0.06 (0.02 to 0.11) 0.05 (0.01 to 0.10)</td>
</tr>
<tr>
<td>P value for trend</td>
<td>.001 &lt;.001</td>
<td>&lt;.001 &lt;.001</td>
<td>.001 .005</td>
</tr>
<tr>
<td>Baseline L-PVS location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White matter (n = 75)</td>
<td>6 1.96 (0.90 to 4.25) 1.88 (0.86 to 4.08)</td>
<td>22 1.64 (1.14 to 2.34) 1.61 (1.13 to 2.31)</td>
<td>0.03 (-0.02 to 0.09) 0.03 (-0.02 to 0.08)</td>
</tr>
<tr>
<td>Basal ganglia (n = 349)</td>
<td>34 2.66 (1.81 to 3.90) 2.53 (1.72 to 3.72)</td>
<td>85 1.38 (1.12 to 1.69) 1.33 (1.08 to 1.64)</td>
<td>0.04 (0.01 to 0.07) 0.03 (0.01 to 0.06)</td>
</tr>
</tbody>
</table>

Abbreviations: L-PVSs, large perivascular spaces; MRI, magnetic resonance imaging; WMH, white matter hyperintensity.

* The WMH volume progression was defined as the difference between WMH volume at 5-year follow-up and baseline. A positive change indicated progression; the progression of WMH volume was natural log transformed. A regression coefficient of 0.04 was interpreted as a 4% increase in the geometric mean of WMH volume progression relative to the reference group.

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mixed L-PVSs in both locations, n = 42). The cumulative incidence of SVD and dementia is listed in the eResults in the Supplement.

L-PVSs and Incident SVD

The presence of L-PVSs at baseline was associated with an increased risk of incident subcortical infarcts and microbleeds and greater WMH progression (model 1) (Table 2). For each SVD marker, the number of L-PVSs increased: both 1 and 2 or more L-PVSs were associated with increased risk of incident subcortical infarcts and microbleeds and promoted a greater WMH progression, with the associations being strongest for 2 or more L-PVSs. When stratified according to L-PVS location, associations with subcortical infarcts and WMHs were found for basal ganglia L-PVSs, whereas an association with incident microbleeds was found for white matter and basal ganglia L-PVSs. When further adjusted for major cardiovascular risk factors, stroke, and APOE4 genotype (model 2), all associations persisted except for the association between 1 L-PVS and WMH progression. There were no interactions of L-PVSs with any of the covariates.

L-PVSs, Cognitive Decline, and Dementia

The presence of L-PVSs was associated with a steeper decline in information processing speed (model 1) (Table 3). Participants with 2 or more L-PVSs had the greatest decline in processing speed compared with those with no L-PVSs, with an intermediate decline for participants with 1 L-PVS. Furthermore, an association with processing speed was found for basal ganglia L-PVSs. In the fully adjusted models, these estimates were attenuated for the presence of increasing L-PVS number. No association of L-PVSs was found for memory or executive function.

In the fully adjusted model, the presence of L-PVSs was associated with an increased risk of developing VaD (model 1: aRR, 4.19; 95% CI, 1.81-9.69; P < .001; model 2: aRR, 3.34; 95% CI, 1.41-7.93; P = .006) but not with all-cause dementia (model 1: aRR, 1.47; 95% CI, 1.00-2.18; P = .06; model 2: aRR, 1.32; 95% CI, 0.89-1.97; P = .18) or Alzheimer disease (model 1: aRR, 1.23; 95% CI, 0.75-2.03; P = .44; model 2: aRR, 1.16; 95% CI, 0.66-2.05; P = .62). The presence of a single L-PVS or basal ganglia L-PVS was associated with a higher incidence of VaD (eFigure 2 and eFigure 3 in the Supplement).

Discussion

In the general population of older individuals free of prevalent dementia at baseline, we found that the presence of L-PVSs was associated with new subcortical infarcts, microbleeds, and WMH progression during a 5-year period. Furthermore, compared with individuals with no L-PVSs, those with
Perivascular spaces follow the course of the penetrating arterioles and are important drainage conduits for cerebral interstitial fluid, solutes, and metabolic waste into the ventricles and for inflammatory and immunologic processes. Some studies suggest that PVSs may be an epiphenomenon and a precursor of SVD. For example, WMHs tend to form around PVSs, and thus PVSs have been speculated to be an imaging biomarker for early alteration of arteriolar wall and blood-brain barrier function that may eventually lead to hemosiderin leakage and lesions in the perivascular parenchyma. Although the association between L-PVSs and SVD progression provides support for such a notion, we also found that the presence of SVD markers at baseline was significantly associated with incident L-PVSs, suggesting the challenges in determining temporality among these lesions. This observed bidirectional association in our study implies the complex interplay between L-PVSs and SVD markers and further strengthens the notion that shared microvascular pathways are involved to mediate the interplay. One potential mechanism is that the structural changes in the microvascular wall could gradually impair the external drainage of the interstitial fluid, and thus PVSs have been speculated to be an imaging biomarker for early alteration of arteriolar wall and blood-brain barrier function that may eventually lead to hemosiderin leakage and lesions in the perivascular parenchyma.
which are driven mainly by hypertensive arteriopathy that affects deep perforators.7-10 The association with incident microbleeds remains significant for L-PVSs in both locations. The spatial distribution of microbleeds reflects specific microvascular pathologic findings (ie, hypertensive arteriopathy and CAA), and the presence of cortical microbleeds or multiple strictly lobar microbleeds is a perceptive neuroimaging marker of CAA.34,36 The CAA that affects the parent leptomeningeal or cortical arteries that supply the subcortical white matter may underlie the link between white matter L-PVSs and microbleeds.37,38 However, the lack of an association of white matter L-PVSs with incident subcortical infarcts or WMH progression could be potentially attributable to low statistical power.

The associations of L-PVSs with a greater decline in processing speed and higher risk of VaD were independent of MRI markers of cerebrovascular disease, suggesting that they were not simply attributable to confounding by other vascular mechanisms. Furthermore, the associations remain significant for L-PVSs in basal ganglia. Our findings are consistent with the hypothesis that SVD contributes to a profile of vascular-related cognitive impairment2,39 and suggest that L-PVSs may be part of the pathologic spectrum that links hypertension and arteriosclerosis to VaD. Alternatively, the observed associations could be secondary to inflammatory cell accumulation and microglial activation,1,40,41 which may be another common pathophysiologic mechanism shared by L-PVSs and cognitive deterioration. However, additionally controlling for circulating C-reactive protein or white blood cell count did not alter these associations.

Strengths and Limitations

Major strengths of the present study include the large population-based sample of older individuals free of dementia at baseline and followed up for a mean of 5 years, the use of standard MRI and reliable assessment of MRI lesions, and the extensive characterization of participants that enabled us to adjust for a series of potential confounders. Our study has several limitations. First, cohort members included in the analysis were younger, more educated, and healthier at baseline than those with missing data (eTable 1 in the Supplement). Individuals with worse vascular risk profile or more severe SVD (those more likely to develop cognitive decline and dementia) died or were lost to follow-up before they could be recruited into the follow-up examination. This attrition may affect our estimates. If those excluded were similarly affected by L-PVSs as those included in the analysis, the significance of results would have been underestimated. Second, there has been no established criterion standard methodologic approach for PVS visual rating.3 Although we took into account the 2013 guidelines on Standards for Reporting Vascular Changes on Neuroimaging16 in defining L-PVSs, our L-PVS scale was developed in house in 2004; thus, it differs in several ways from more recent research. Additional cross-validation and reliability studies are needed. In particular, our protocol did not allow us to capture smaller PVSs. Third, similar to other commonly used scales, we did not include L-PVSs in the substantia innominate for basal ganglia rating. Fourth, the pathologic features of L-PVS are progressive in nature, and the cutoff in L-PVS number is not easily chosen. Furthermore, the cutoff of abnormal size is arbitrary, and the actual border between normal and abnormal PVSs may not be the same in different brain regions. Fifth, despite the meticulous efforts by trained graders, the potential misclassification of L-PVSs vs lacunes or subcortical infarcts is unavoidable. For example, although subcortical infarcts on FLAIR generally have a hyperintense rim, the rim is not always present.15 The use of a 4-mm size criterion for infarcts may have resulted in some misclassification of infarcts as PVSs.16 To better visualize smaller and large PVSs along the vascular trunk for differential diagnosis with lacunes, future studies are needed that are based on quantitative techniques instead of visual rating scale12 and on a 3-dimensional coregistered multisequence MRI analysis.

Conclusions

Large PVSs mark the progression of SVD and are associated with cognitive decline and VaD in older individuals. From a clinical perspective, our findings strengthen the notion that L-PVSs serve as an MRI marker of SVD and suggest that L-PVSs (and the pathomechanisms leading to their dilatation) could be a potential target for therapies and prevention strategies of SVDs and vascular-related cognitive impairment.
manuscript; and the decision to submit the manuscript for publication.

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