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Journal

Journal of Alzheimers Disease, 96(1)

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Publication Date

2023

DOI

10.3233/JAD-230445

Peer reviewed

MRI Visible Perivascular Spaces and the Risk of Incident Mild Cognitive Impairment in a Community Sample

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Abstract

Background: Magnetic resonance imaging (MRI) visible perivascular spaces (PVS) are associated with the risk of incident dementia but their association with the early stages of cognitive impairment remains equivocal.

Objective: We examined the association between MRI visible PVS and the risk of incident mild cognitive impairment (MCI) in the community-based Framingham Heart Study (FHS).

Methods: FHS participants aged at least 50 years free of stroke, cognitive impairment, and dementia at the time of MRI were included. PVS were rated according to severity in the basal ganglia and centrum semiovale (CSO) using established criteria. Cox regression analyses were used to relate PVS to incident MCI adjusted for demographic and cardiovascular variables.

Results: The mean age of the sample (1,314 participants) at MRI was 68 years (SD, 9; 54% women). There were 263 cases of incident MCI over a median 7.4 years follow-up (max, 19.8 years). MCI risk increased with higher PVS severity in the CSO. Relative to persons with the lowest severity rating, persons with the highest severity rating in the CSO had a higher risk of incident MCI (hazard ratio [HR] = 2.55; 95% confidence interval [CI], 1.48–4.37; p = 0.0007).

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In secondary analysis, this association seemed stronger in women. Risk of incident MCI was nominally higher for participants with the highest severity grade of PVS in the basal ganglia, though not statistically significant relative to the lowest grade (HR = 2.19; 95% CI, 0.78–6.14; $p =$ 0.14).

Conclusions: PVS burden in the CSO may be a risk marker for early cognitive impairment.

Keywords

Alzheimer's disease; cerebral small vessel disease; magnetic resonance imaging; mild cognitive impairment; perivascular spaces

INTRODUCTION

Perivascular spaces (PVS) are the interstitial fluid passageways that surround brain vasculature responsible for nutrient supply, collectively forming part the neurovascular unit and the blood-brain barrier [1, 2]. PVS have an important role in glymphatic clearance, providing routes for the flow and drainage of macroscopic waste [3, 4], where such waste might otherwise accumulate and have neurotoxic effects [3, 5].

Magnetic resonance imaging (MRI) visible PVS are considered a sign of neurovascular dysfunction [6, 7] and prevalently occur in the centrum semiovale (CSO) and basal ganglia (BG) in cerebral small vessel disease (CSVD) and neurodegenerative diseases such as Alzheimer's disease [8, 9]. The presence of MRI visible PVS has also been associated with poorer cognitive performance in a memory clinic population, most of whom had mild cognitive impairment (MCI) or dementia [10, 11], but this association was not found in a meta-analysis of population-based cohorts without dementia [12].

Although an association between MRI visible PVS and cognitive performance remains equivocal in healthy individuals, recent literature suggests that higher counts of MRI visible PVS in both the BG and CSO are associated with an increased risk of cognitive decline and incident dementia [13–15]. Few studies have shown that PVS counts are elevated in those with MCI [16, 17] but, to our knowledge, there has not yet been investigation into whether the burden of MRI visible PVS are associated with an increased risk of incident MCI, which can be a transitional state prior to the development of dementia.

This study aimed to investigate the association between MRI visible PVS and the risk of incident MCI in a large community-based sample. We hypothesized that greater PVS counts in the BG and CSO would be associated with an increased risk of incident MCI.

METHODS

Sample

We studied participants from the Framingham Heart Study (FHS), a large community-based prospective cohort that recruited from the community in Framingham, MA, USA. Launched in 1948, the original mission of the FHS was to investigate the epidemiology of cardiovascular disease [18]. Since, the FHS has evolved into multiple cohorts, for which two

were utilized for present analysis: the Original cohort [18] and the Offspring cohort [19]. The Original cohort consists of 5209 adults who completed initial assessment between 1948 and 1953 with follow-up approximately every two years thereafter. The Offspring cohort consists of 5,124 adults who were the children of the first-generation cohort or spouses of these children. The participants were enrolled between 1971 and 1975, with follow-up approximately every four years thereafter.

Participants were invited to undergo brain MRI as part of an ancillary study on neuropsychological testing and brain imaging. Brain MRIs were obtained during exams 25–31 in the Original cohort and 7–9 in the Offspring cohort. For the present study, we included participants who attended the clinic exams corresponding to the brain MRIs and had PVS ratings. Participants were excluded if, at baseline (time of MRI), they were aged less than 50 years, had a diagnosis of dementia, MCI, or other significant neurological disease that manifests on MRI scans (e.g., traumatic brain injury, stroke) or if they were not followed up for MCI. Figure 1 details sample selection. All participants provided written informed consent. The Institutional Review Board of Boston University Medical Center approved the study.

Brain MRI and PVS rating

Participants underwent brain MRI imaging with a 1T (this occurred between 1999–2005) or 1.5T (after 2005) magnetom scanner [20]. The 1T MRI used a T2-weighted double spin echo coronal imaging sequence of 4 mm contiguous slices. The 1.5T MRI used a T2-weighted double spin-echo coronal imaging sequence of 3 mm contiguous slices [20]. Acquisition and imaging processing details have been published previously [21–23].

PVS were determined using the STandards for ReportIng Vascular changes on nEuroimaging Criteria (STRIVE) consensus criteria [9, 15]. Briefly, PVS had to display signal intensity similar to cerebrospinal fluid, follow the course of penetrating vessels, and have a diameter less than 3 mm.

Visible PVS were rated by three study investigators (neuroradiologist, vascular neurologist, and a well-trained research assistant) who were blind to all participant information. We grouped PVS according to their brain topography, involving the CSO and BG [24]. Ratings were performed on T2-weighted axial MRI sequences, to the extent possible. Following our previous approach,[15] PVS burden was categorized into grades based on PVS counts: I (1–10), II (11–20), III (20–40) and IV (>40).

We have previously reported the intra and inter-rater reliability of PVS ratings (ICC ranging from 0.74 to 0.81 for intra-rater reliability, and 0.80 to 0.90 for inter-rater reliability) [6].

MCI case ascertainment

Participants in the FHS are under continuous and uninterrupted surveillance for the incidence of cognitive impairment and dementia. Participants complete the Mini-Mental State Examination (MMSE) at each examination cycle as a cognitive screen [25]. Participants also complete more extensive neuropsychological testing via several ancillary studies. Using the MMSE, participants are flagged with suspected cognitive impairment

if 1) performance falls below education-based thresholds, 2) we observe a decline of 3 or more points between consecutive examinations, or 3) we observe a decrease of 5 or more points from the participant's highest past MMSE score. We also flag participants with suspected cognitive impairment following referrals or concern expressed by the participant, their family, or primary care physician. Once flagged, participants complete annual regular neuropsychological and neurologic evaluations until they develop dementia or are adjudicated to be normal. Evaluations indicative of possible cognitive impairment are followed by referral to our study dementia review committee, comprising a neurologist and neuropsychologist. The dementia review committee adjudicates a diagnosis of MCI in accordance with the criteria defined by Petersen et al. [26], which defined impairment as performance on a single cognitive test within a domain greater than 1.5 SD below normative expectations. Participants are classified into subtypes depending on single or multiple domain impairment and amnestic (only memory domain impaired) or non-amnestic subtypes (memory domain not impaired). We included any MCI in the present study.

Statistical analyses

We used Cox proportional hazard regression models to investigate the association between PVS burden and the incidence of MCI. Kolmogorov-type supremum tests were used to assess the proportional hazards assumption [27]. Follow-up for MCI was from the time of brain MRI to incident MCI through to 2018 (median, 7.4 years; Q1–Q3, 4.9–13.2; max 19.8). For persons without incident MCI, follow-up was censored at the time of death or the date the participant was last known to be MCI-free, also through to 2018. PVS in the CSO and BG (grades I-IV) were modelled separately as categorical predictors with grade I as the reference group. Additionally, we created a categorical mixed PVS score that captured high burden (grade III or IV PVS) in neither region, strictly in the CSO, strictly in the BG, or both regions (0 = none, 1 = BG region only, 2 = CSO region only, or 3 = both regions), with score 0 as the reference group.

All models were adjusted for age at brain MRI, sex, the time interval between the brain MRI and exam, FHS cohort, education, current smoking, diabetes, hypertension, and prevalent cardiovascular disease. These covariates were chosen to control for confounding based on *a priori* based on knowledge of the literature and cohort. In a sensitivity analysis, we included additional adjustments for common imaging features of small vessel disease. In the first sensitivity analysis, we added an adjustment for white matter hyperintensity volume as a percentage of intracranial volume. In a second sensitivity analysis, we included an additional adjustment for cerebral brain infarcts. The purpose of these analyses was to determine if the associations between PVS and incident MCI were independent of other common CSVD imaging features. Adjustment for image view (coronal versus axial) did not change inferences and thus was not included in the statistical models. In a post-hoc analysis, we stratified associations between PVS and incident MCI by sex. This was because a previous cross-sectional study reported that PVS volume fraction in the CSO was higher in patients with MCI, versus controls, in women only [28].

MRI scanner strength is reflected on the image view used (coronal/axial) in this sample. Adjustment this variable did not change inferences and thus was not included in the statistical models.

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). A *p*-value<0.05 was considered statistically significant.

RESULTS

Sample characteristics

Table 1 displays the sample demographics, stratified by PVS burden severity. Of the 1314 participants, we observed 263 (20%) cases of incident MCI. Across the sample, the mean age was 68 years (SD, 9) and 54% were female. Overall, 4.8% and 0.3% of the sample had the highest grade of PVS severity in the CSO and BG, respectively. Those participants with the lowest PVS severity ratings tended to be younger, more highly educated, and have the lowest prevalence of cardiovascular disease.

Participants with available PVS ratings ($n = 2,019$) were compared with those excluded due to missing PVS ratings ($n = 2,945$). Overall, they were of similar age, sex and risk factor profile except for lipid lowering treatment and triglyceride levels; the latter was missing in 19% of the sample which may have skewed the results but considered unlikely to bias substantially the results.

PVS and incident MCI

Supremum tests showed no deviations from the proportional hazards assumption. The risk of MCI tended to increase with increasing PVS severity in the BG (Table 2). However, relative to the lowest severity rating, only those with a severity rating of 2 displayed a statistically significant increase in MCI risk, perhaps owing to the low number of incident cases in the highest severity groups.

The risk of incident MCI also increased with increasing severity of PVS in the CSO (Table 2). Relative to persons with the lowest severity rating, persons with ratings of 3 and 4 both displayed a higher risk of incident MCI. The increase in MCI risk was 2.55-fold in those with the highest severity of PVS in the CSO.

When capturing high burden (grade III or IV PVS) in neither region (reference), strictly in the CSO, strictly in the BG, or both regions (BG and CSO), we observed a higher risk of incident MCI only for those with a high PVS burden in the CSO (Table 2).

We explored whether the associations between PVS and incident MCI were independent of premorbid cognitive function. To investigate this, we included an additional adjustment for Wide Range Achievement Test (WRAT) scores, which is a common neuropsychological tool to assess premorbid cognitive function. Additional inclusion of WRAT scores to the multivariable adjusted model did not alter our results: Compared with the reference grade I CSO, the relation with incident MCI remained unchanged for grades 2 (HR 1.33, 95% CI 0.92, 1.9), grade 3 (HR 1.65, 95% CI 1.09, 2.52) or 4 (HR 2.84, 95% CI 1.68, 4.8); similar

results were observed for BG region were grade 2 (HR 1.55, 95% CI 1.16, 2.09), grade 3 (HR 1.53, 95% CI 1.02, 2.27), and grade 4 (HR 2.44, 95% CI 0.96, 6.19) results were largely unchanged.

In addition, we performed a proportional subdistribution hazard regression using death as a competing risk, observing attenuation of associations with high BG PVS burden, while the associations of CSO PVS burden with MCI remained significant and largely unchanged.

Consideration of additional factors such as lipid levels (total cholesterol, low density, and high-density lipoprotein) in multivariable models did not change inferences.

Sensitivity analyses

Further adjustment for white matter hyperintensity volume attenuated the findings for the BG, such that there were no differences in risk of incident MCI between severity groups (Table 3). In contrast, persons with the highest grade of PVS in the CSO continued to display a higher risk of incident MCI, although the magnitude of effect was attenuated. Similarly, in the mixed region analysis, only persons with a high severity of PVS in the CSO displayed a higher risk of incident MCI. Results were similar to the primary models after including an additional adjustment for cerebral brain infarcts.

Post-hoc analysis of sex differences

The association between each grade of PVS severity in the CSO and incident MCI was more pronounced in women than in men (Table 4). For example, women with a PVS rating of IV in the CS, versus a rating of I, had a 3.49-fold increase in MCI risk. In contrast, men with a PVS rating of IV in the CS, versus a rating of I, had a 2.48-fold increase in MCI risk. For the higher grades of PVS severity in the BG, there were too few cases to permit a meaningful comparison between men and women. When capturing high burden (grade III or IV PVS) in neither region (reference), strictly in the CSO, strictly in the BG, or both regions (BG and CSO), results were relatively similar between males and females.

DISCUSSION

We studied the association between PVS visible on MRI and the risk of incident clinical MCI over a median 7.4-year follow-up period in a prospective community-based cohort. Overall, we observed that higher severity of PVS in the CSO was associated with a higher risk of incident MCI. Greater severity of PVS in the BG was nominally associated with a higher risk of incident MCI. However, the effect was not statistically significant for the highest grades of severity, which may be attribute to the small number of incident MCI cases within these strata (only 4 cases were observed in the high severity group). The associations between CSO PVS burden and the risk of incident MCI remained after adjustment for common imaging features of cerebral small vessel disease. Therefore, these data suggest that a higher burden of MRI visible PVS in the CSO are associated with a higher risk of early clinical cognitive impairment, independent of cardiovascular disease risk factors and common imaging features.

Although greater PVS burden has been associated with a higher risk of incident dementia, previous evidence for an association between PVS burden and early stages of cognitive dysfunction has been mixed [12–15]. We have previously reported that greater PVS severity is associated with a higher risk of incident dementia in the FHS [29]. The current study extends these findings to an early stage of cognitive dysfunction. Taken together, these data suggest that a higher burden of PVS in the CSO is associated with an increased risk of early-stage cognitive impairment leading to dementia.

A previous cross-sectional study reported that the PVS volume fraction of white matter in the CSO was higher in persons with MCI as compared to controls, an effect driven by women [28]. We also observed that the associations between CSO PVS severity and incident MCI was nominally stronger in women as compared to men. The reasons underlying this potential sex difference are unclear and require further study. Although male sex has been associated with having a higher burden of PVS in the CSO [30], this was not the case in the present study; Regarding PVS severity in the CSO, males in this study were slightly overrepresented in the lowest PVS grade category (53% male) and underrepresented in the highest grade category (41% male). However, in view of the frequently mixed etiology of MCI, addressing sex differences in the relation of PVS burden and MCI is complex and will require further studies with larger samples addressing subtypes of MCI.

Aside from sex, several other clinical and demographic factors have been associated with a higher PVS count in the CSO, including age, more education, higher blood pressure, and higher HDL cholesterol [30]. Other small vessel disease markers, including white matter hyperintensities and lacunes have also been associated with a higher burden of PVS in the CSO [30]. The prospective, population-based Age, Gene/Environment Susceptibility–Reykjavik Study reported that the presence of large PVS was associated with new subcortical infarcts, microbleeds, and WMH progression during a 5-year follow-up [14], suggesting MRI-visible PVS as an early-stage marker for cerebral small vessel disease. Thus, although causality remains to be determined, prevention of PVS enlargement through management of vascular risk factors may help to lower the risk of vascular brain injury and vascular cognitive impairment, particularly in women.

The topography of PVS visible on MRI has been suggested to represent different subtypes of CSVD, high CSO PVS burden representing cerebral amyloid angiopathy, high burden BG PVS representing hypertensive arteriopathy and high burden in both regions reflecting either the combined effects of both arteriopathies or advanced hypertensive arteriopathy. Our results suggest that both arteriopathies are related to higher risk of MCI although statistical significance was reached only for high CSO PVS burden likely due to the larger number of events in this subgroup. The relation further suggested a dose effect relation with higher hazards as PVS burden increased in either region.

Strengths of the current study include the community-based sample and the rigorous and uninterrupted surveillance for incident MCI. However, the current study was not without limitations. Firstly, of those with a high number of PVS counts in the BG, we had a relatively small number of incident MCI cases and may have been underpowered to detect effects. Second, our sample was mostly Caucasian. Replication in other samples

is warranted. Third, we assessed for possible selection bias comparing the sample of participants included to those excluded without PVS measurements, observing similar demographic and clinical characteristics, overall considered unlikely to bias the results substantially.

In conclusion, the current study provides support for PVS burden in the CSO as a marker for early cognitive impairment leading to dementia. Detection of high burden of MRI visible PVS may prompt clinicians to increase surveillance for cognitive disorders. Future studies will address mechanisms underlying the associations of PVS with cognitive disorders, which may help in identification of treatment targets and preventive efforts.

ACKNOWLEDGMENTS

DATA AVAILABILITY

Data from this manuscript may be shared with qualified investigators following FHS data sharing procedures outlined at https://www.framinghamheartstudy.org/.

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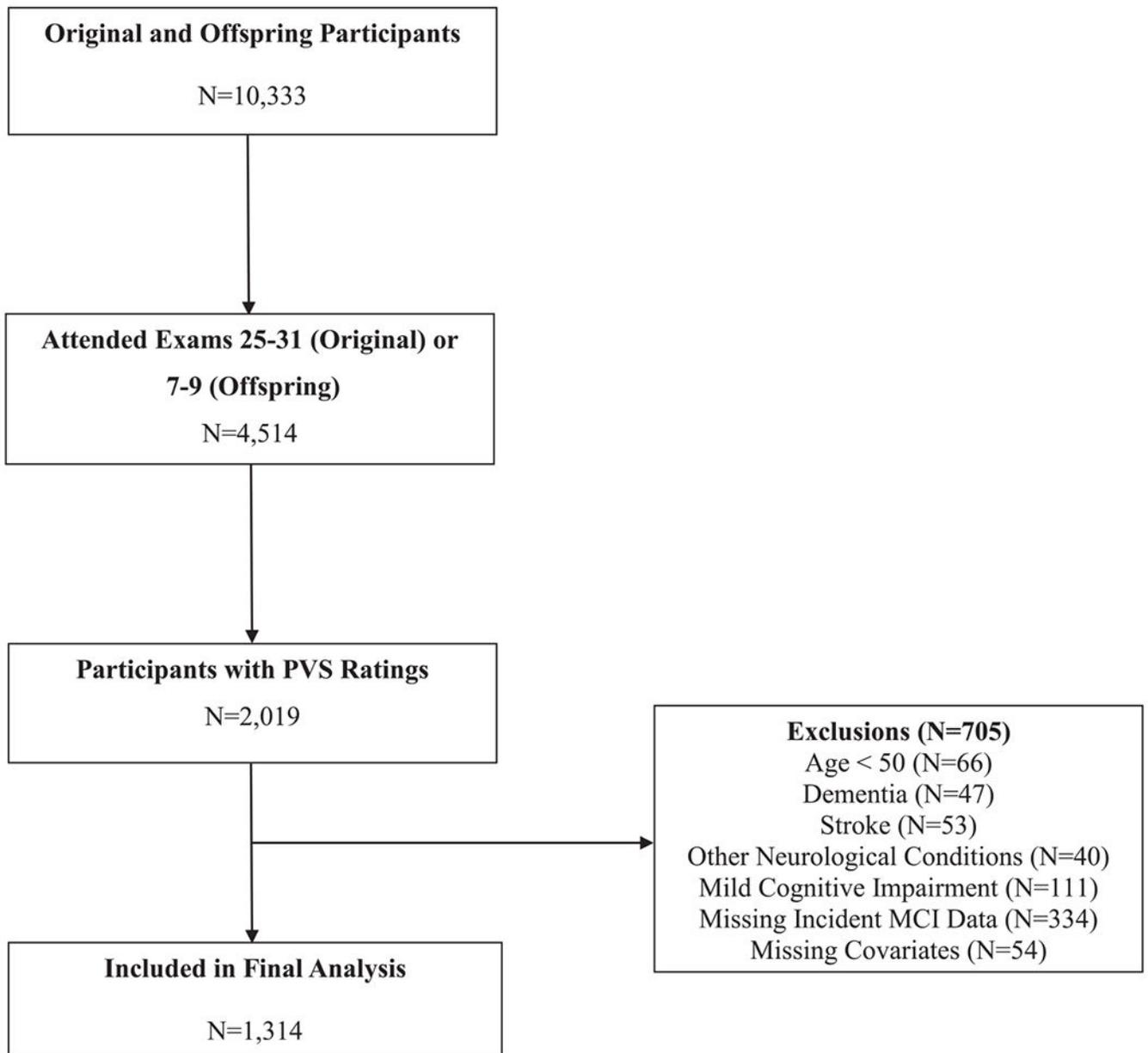
Fig. 1.
Study flow diagram.

Table 1

Cohort characteristics across PVS severity ratings

	Total	Centrum Semiovale PVS Severity				Basal Ganglia PVS Severity			
		I	II	III	IV	I	II	III	IV
N	1,314	397	615	239	63	630	545	128	11
Age (y) at MRI, mean (SD)	68 (9)	63 (8)	69 (9)	74 (9)	77 (8)	64 (8)	71 (9)	77 (7)	79 (6)
Time interval* (y), mean (SD)	0.9 (1.0)	0.9 (0.9)	1.0 (1.0)	0.8 (1.0)	0.7 (1.1)	1 (0.9)	0.9 (1)	0.7 (1)	0.7 (0.8)
Male, n (%)	601 (46)	209 (53)	290 (47)	76 (32)	26 (41)	310 (49)	238 (44)	49 (38)	4 (36)
FHS Cohort, n (%)									
Original	115 (9)	0 (0)	48 (8)	49 (21)	18 (29)	13 (2)	63 (12)	36 (28)	3 (27)
Offspring	1199 (91)	397 (100)	567 (92)	190 (79)	45 (71)	617 (98)	482 (88)	92 (72)	8 (73)
Education, n (%)									
Less than high school	49 (4)	10 (3)	19 (3)	14 (6)	6 (10)	11 (2)	26 (5)	12 (9)	0 (0)
High school	403 (31)	107 (27)	191 (31)	82 (34)	23 (37)	184 (29)	171 (31)	43 (34)	5 (45)
Some college	354 (27)	106 (27)	163 (27)	69 (29)	16 (25)	169 (27)	145 (27)	37 (29)	3 (27)
College	508 (39)	174 (44)	242 (39)	74 (31)	18 (29)	266 (42)	203 (37)	36 (28)	3 (27)
SBP (mmHg), mean (SD)	128 (18)	123 (16)	129 (18)	133 (20)	134 (18)	125 (17)	130 (19)	134 (19)	138 (18)
DBP (mmHg), mean (SD)	73 (10)	74 (9)	73 (10)	71 (10)	73 (11)	74 (9)	72 (10)	71 (11)	73 (9)
Hypertension[a], n (%)	675 (51)	144 (36)	332 (54)	153 (64)	46 (73)	248 (39)	323 (59)	93 (73)	11 (100)
Hypertension treatment, n (%)	540 (41)	118 (30)	269 (44)	116 (49)	37 (59)	188 (30)	260 (48)	83 (65)	9 (82)
Current smoker, n (%)	105 (8)	33 (8)	48 (8)	17 (7)	7 (11)	53 (8)	44 (8)	8 (6)	0 (0)
Diabetes, n (%)	174 (13)	41 (10)	93 (15)	32 (13)	8 (13)	67 (11)	89 (16)	15 (12)	3 (27)
Diabetes treatment, n (%)	103 (8)	21 (5)	58 (9)	19 (8)	5 (8)	36 (6)	58 (11)	8 (6)	1 (9)
Anti-lipid treatment, n (%)	416 (32)	106 (27)	207 (34)	80 (33)	23 (37)	169 (27)	191 (35)	51 (40)	5 (45)
CVD, n (%)	209 (16)	32 (8)	113 (18)	53 (22)	11 (17)	58 (9)	110 (20)	38 (30)	3 (27)
APOE e4 carrier, n (%)	288 (22)	93 (24)	128 (21)	52 (22)	15 (24)	135 (22)	124 (23)	26 (21)	3 (27)
WMHV (% of ICV), mean (SD)	0.2 (0.4)	0.1 (0.1)	0.2 (0.3)	0.4 (0.6)	0.6 (0.6)	0.1 (0.1)	0.2 (0.3)	0.6 (0.7)	1.4 (0.7)
CBI, n (%)	158 (12)	22 (6)	75 (12)	44 (18)	17 (27)	46 (7)	67 (12)	40 (31)	5 (45)

CBI, cerebral brain infarct; CVD, prevalent cardiovascular disease; DBP, diastolic blood pressure; FHS, Framingham Heart Study; ICV, intracranial volume; MRI, magnetic resonance imaging; PVS, perivascular spaces; SBP, systolic blood pressure; SD, standard deviation; WMHV, white matter hyperintensity volume.

[a] Hypertension is defined as SBP 140 mmHg or DBP 90 mmHg and/or use of antihypertensive medication.

*Time interval between clinical exam and brain MRI.

Table 2

Associations between PVS by region and risk of incident MCI

Region	Group	Events	N	HR	95% CI	p
Basal Ganglia (BG)						
	I (ref)	83	630	–	–	–
	II	**131**	**545**	**1.46**	**1.08–1.98**	**0.01**
	III	45	128	1.42	0.94–2.17	0.10
	IV	4	11	2.19	0.78–6.14	0.14
Centrum Semiovale (CSO)						
	I (ref)	46	397	–	–	–
	II	113	615	1.32	0.92–1.89	0.14
	III	**79**	**239**	**1.82**	**1.20–2.77**	**0.005**
	IV	**25**	**63**	**2.55**	**1.48–4.37**	**0.0007**
Mixed Regions[1]						
	Neither (ref)	144	964	–	–	–
	BG only	15	48	1.36	0.78–2.37	0.28
	CSO only	**70**	**211**	**1.74**	**1.28–2.38**	**0.0005**
	CSO and BG	34	91	1.40	0.92–2.14	0.11

BG, basal ganglia; CI, confidence interval; CSO, centrum semiovale; FHS, Framingham Heart Study; HR, hazard ratio; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PVS, perivascular spaces. Models adjusted for age at MRI, sex, interval between the brain MRI and exam, education, FHS cohort, current smoking, diabetes, hypertension, and prevalent cardiovascular disease.

[1] High burden (grade III or IV PVS) in neither region, strictly in the basal ganglia, or both regions (basal ganglia and centrum semiovale).

Table 3

Sensitivity analyses showing associations between PVS and risk of incident MCI, with additional adjustment for imaging features

Region	Group	Events	N	HR	95% CI	p
Model 1 *+WMHV						
BG		263	1309			
	I (ref)	83	626	–	–	–
	II	131	544	1.27	0.93–1.73	0.13
	III	45	128	0.99	0.63–1.56	0.96
	IV	4	11	1.15	0.39–3.37	0.80
CSO		263	1314			
	I (ref)	46	393	–	–	–
	II	113	614	1.20	0.83–1.73	0.33
	III	79	239	1.40	0.90–2.19	0.14
	IV	25	63	**1.91**	**1.09–3.36**	**0.02**
Mixed Regions[1]		263	1309			
	Neither (ref)	144	959	–	–	–
	BG only	15	48	1.09	0.62–1.92	0.77
	CSO only	70	211	**1.44**	**1.04–1.99**	**0.03**
	Both regions	37	91	0.95	0.60–1.51	0.83
Model 1 *+any CBI						
BG		263	1314			
	I (ref)	83	630	–	–	–
	II	131	545	**1.46**	**1.08–1.97**	**0.01**
	III	45	128	1.40	0.92–2.14	0.12
	IV	4	11	2.12	0.75–5.98	0.16
CSO		263	1314			
	I (ref)	46	397	–	–	–
	II	113	615	1.31	0.91–1.89	0.14
	III	79	239	**1.81**	**1.19–2.76**	**0.006**
	IV	25	63	**2.51**	**1.46–4.33**	**0.0009**
Mixed Regions[1]		263	1314			

Region	Group	Events	N	HR	95% CI	p
	Neither (ref)	144	964	–	–	–
	BG only	15	48	1.34	0.77–2.34	0.31
	CSO only	70	211	**1.73**	**1.27–2.36**	**0.0005**
	Both regions	34	91	1.38	0.90–2.11	0.14

BG, basal ganglia; CBI, cerebral brain infarcts; CI, confidence interval; CSO, centrum semiovale; FHS, Framingham Heart Study; HR = hazard ratio; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PVS, perivascular spaces; WMHV, white matter hyperintensity volume.

*
Model 1 adjusts for age at MRI, sex, interval between the brain MRI and exam, education, FHS cohort, current smoking, diabetes, hypertension, and prevalent cardiovascular disease.+each imaging feature specified in the table.

[1]
High burden (grade III or IV PVS) in neither region, strictly in the centrum semiovale, strictly in the basal ganglia, or both regions (basal ganglia and centrum semiovale).

Table 4

Associations between PVS by region and risk of incident MCI stratified by sex

Region	Men					Women				
	Events	N	HR	95% CI	p	Events	N	HR	95% CI	p
BG										
1 (ref)	43	310	–	–	–	40	320	–	–	–
2	49	238	1.27	0.80–2.00	0.31	82	307	**1.67**	**1.10–2.54**	**0.02**
3	13	49	1.52	0.76–3.06	0.24	32	79	1.54	0.89–2.67	0.12
4	2	4	**5.09**	**1.10–23.55**	**0.04**	2	7	1.31	0.31–5.61	0.71
CS										
1 (ref)	31	209	–	–	–	15	188	–	–	–
2	50	290	1.10	0.67–1.78	0.71	63	325	**1.84**	**1.02–3.30**	**0.04**
3	16	76	1.34	0.70–2.56	0.37	63	163	**2.60**	**1.38–4.89**	**0.003**
4	10	26	**2.48**	**1.11–5.57**	**0.03**	15	37	**3.49**	**1.58–7.72**	**0.002**
Mixed[1]										
Neither (ref)	74	476	–	–	–	70	488	–	–	–
BG only	7	23	1.43	0.63–3.28	0.39	8	25	1.41	0.65–3.06	0.38
CSO only	18	72	1.53	0.89–2.62	0.12	52	139	**1.86**	**1.25–2.78**	**0.002**
Both regions	8	30	1.69	0.78–3.65	0.18	26	61	1.39	0.83–2.35	0.21

BG, basal ganglia; CI, confidence interval; CSO, centrum semiovale; FHS, Framingham Heart Study; HR, hazard ratio; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PVS, perivascular spaces. Models adjusted for age at MRI, sex, interval between the brain MRI and exam, education, FHS cohort, current smoking, diabetes, hypertension, and prevalent cardiovascular disease.

[1] High burden (grade III or IV PVS) in neither region, strictly in the centrum semiovale, strictly in the basal ganglia, or both regions (basal ganglia and centrum semiovale).