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Association of MRI Visible Perivascular Spaces and Neurofilament Light Chain: The Framingham Heart Study

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Abstract

Background: Neurofilament light chain (NfL) is a marker of neuronal injury. Perivascular spaces (PVS) visible on magnetic resonance imaging (MRI) represent cerebral small vessel disease (CSVD) but their role as markers of neuronal injury needs further clarification.

Objective: To relate PVS burden according to brain topography and plasma NfL.

Methods: Framingham Heart Study (FHS) participants with brain MRI and NfL measurements were included. PVS were rated in the basal ganglia (BG) and centrum semiovale (CSO) using validated methods and categorized based on counts. A mixed region variable representing high burden PVS in either BG or CSO was assessed. Multivariable linear regression analyses were used to relate PVS burden to log-transformed NfL levels in models adjusted for age, sex, FHS cohort, time between MRI and clinic exam, and image view (model 1), vascular risk factors (model 2), and white matter hyperintensity volume, covert brain infarcts, and cerebral microbleeds (model 3).

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CONFLICT OF INTEREST

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All other authors have no conflict of interest to report.

Results: Among 1,457 participants (68.1±8.5 years, 45% males), NfL levels increased with higher PVS burden. Multivariable analysis showed an association of high PVS burden strictly in BG with NfL (β = 0.117, 95% CI 0.014–0.221; $p = 0.027$), but attenuated in model 3. The associations were mainly in participants ≥65 years (β = 0.122, 95% CI 0.015–0.229, $p = 0.026$), women (β = 0.156, 95% CI 0.024–0.288, $p = 0.021$), and *APOE ε*4 non-carriers (β = 0.140, 95% CI 0.017–0.263, $p = 0.026$).

Conclusions: The association of strictly BG high PVS burden with NfL suggests a role for PVS as markers of neuroaxonal injury, but our results are hypothesis generating and require further replication.

Keywords

Alzheimer's disease; basal ganglia; cerebral small vessel disease; MRI visible perivascular spaces; neurofilament light chain; neuroaxonal injury

INTRODUCTION

Neurofilament light chain (NfL) is a subunit of neurofilaments present in dendrites and neuronal bodies that confers structural stability to neurons and axons [1]. Neurofilaments enable radial growth of axons and are highly expressed in large myelinated axons in an age dependent manner [1]. Serum NfL levels increase in response to central nervous system axonal damage from inflammatory, neurodegenerative, or vascular injury [1]. NfL is also an emerging blood and cerebrospinal fluid marker of neuroaxonal damage in various neurological diseases like multiple sclerosis [2], Alzheimer's disease, and more recently cerebral small vessel disease (CSVD) [3]. NfL is associated with deposition of amyloid-β (Aβ) in the leptomeningeal arteries, the hallmark of cerebral amyloid angiopathy (CAA) [4]. Recently, elevated serum NfL has been observed in patients with recent subcortical infarcts and stroke [5]. Both cerebrospinal fluid and serum NfL have been found to be increased in patients with white matter hyperintensities (WMH) and levels correlate with WMH load, a magnetic resonance imaging (MRI) marker for CSVD burden [6].

Perivascular spaces (PVS) visible on brain MRI are markers of CSVD [7] and are associated with neurological disorders including multiple sclerosis [8], dementia [9], and stroke [10]. In a recent report, we found that PVS were associated with incident dementia in Framingham Heart Study (FHS) participants [11], which remained independent of other MRI markers of CSVD. One explanation is that neuronal injury is a neuropathological hallmark in the pathophysiology of dementia. However, whether detection of high burden of PVS reflects neuronal injury in community dwelling individuals free of neurological disease needs further clarification.

PVS may reflect various processes such as CSVD or dysfunction in the more recently described glymphatic system, which may not be related to CSVD. Thus, characterization of PVS as imaging markers of neuronal injury may advance current understanding of the pathophysiology underlying PVS, which in turn may assist to understand further the interplay of plasma and imaging markers of dementia risk. In addition, it may further support NfL as marker of vascular mediated neuronal injury. This may spur further research

into intervention strategies for neurodegenerative diseases at the subclinical stages. To our knowledge, the relation of MRI visible PVS and NfL has not yet been studied.

The aim of our research was to study the relation between PVS and NfL as marker of neuroaxonal damage, considering the topographic location and burden of PVS as they may reflect differing subtypes of CSVD: hypertensive arteriopathy for basal ganglia (BG) and CAA for centrum semiovale (CSO) predominant PVS [12]. We hypothesized that MRI visible PVS are associated with higher NfL levels in our sample of community dwelling participants.

METHODS

Sample

The recruitment of participants in the FHS and MRI acquisition have been previously described [13]. The FHS started in 1948 with the recruitment of the original cohort. This was followed by recruitment of the offspring of the original cohort and spouses of the offspring in 1971. Subsequently, the third generation made up of grandchildren of the original cohort was recruited in 2002. The OMNI 1 cohort representing more ethnic and racial diversity of the town of Framingham was recruited in 1994 as the previous generations were predominately white of European descent. FHS participants are invited for examination every 2–4 years which constitute an examination cycle, and participants undergo brain MRI as part of ancillary studies on brain structure and cognitive outcomes [14, 15]. In this study, we included Offspring and OMNI 1 cohort participants with available brain MRI and NfL measurements. NfL assessment was obtained in FHS Offspring and OMNI 1 participants who attended examination cycles 9 and 4, respectively. Brain MRI occurred during examination cycles 7 through 9 in the Offspring cohort, and examinations 2 through 4 in the OMNI 1 cohort.

Participants with available MRI attending clinic exams 9 and 4 in the Offspring and OMNI 1 cohorts, respectively, who also had NfL assessments, were eligible for this study (N = 1,995). We excluded 483 participants who did not have PVS assessment and 55 due to missing data or history of stroke, dementia, or other neurological conditions that could affect the estimation of PVS. After these exclusions, 1,457 participants were selected for the study. The flow chart of participant selection is shown in Fig. 1.

The Institutional Review Board of Boston University Medical Center approved the study protocol and informed consent was obtained from all participants.

Exposure

Brain MRI and PVS ratings—Details on the brain MRI protocol have been previously reported [13]. We used 1.5 Tesla Magnetom scanner Siemens Medical, Erlangen Germany.

PVS were rated using the standards for reporting vascular changes on Neuroimaging (STRIVE) consortium criteria [16]. PVS are visible spaces on brain MRI, with the same signal intensity as cerebrospinal fluid and accompany perforating vessels as they go through the grey or white matter [17]. They are usually found in the BG, midbrain, and CSO, and

differ from lacunar infarcts by their small breadth (<3 mm) and absence of T2-hyperintense border around the spaces on T2-weighted or FLAIR sequences except when they pass through an area of WMH [17]. Intra- and inter-rater reproducibility of ratings has been previously reported and considered good to excellent [13].

PVS burden was categorized using a previously validated method into grades I-IV in the BG and CSO regions based on PVS counts: grade I (1–10), grade II (11–20), grade III (20–40) and grade IV (>40) [17]. PVS were rated irrespective of the other region (i.e., BG ratings were rated irrespective of CSO ratings and vice versa). In each region, we defined high burden as grades III or IV. The high burden definition was then used to create a categorical variable to describe high burden in mixed brain regions as follows: no high burden in either the BG or CSO, high burden strictly in the BG (i.e., excluding those with concurrent high burden in the CSO), high burden strictly in the CSO (i.e., excluding those with concurrent high burden in the BG), and high burden in both brain regions. It is important to note that the groups denoted strictly in the BG or CSO differ from the groups in the respective regions in that exclusion of cases that have concurrent high burden on both regions, which may allow a clearer representation of the underlying arteriopathy (hypertensive for BG or CAA for CSO).

Cerebral microbleeds, white matter hyperintensities, and covert brain infarcts—We obtained data for cerebral microbleeds, covert brain infarcts and WMH using MRI acquisition and ratings previously described [18, 19]. Cerebral microbleeds were defined according to published guidelines [20] and were categorized as present or absent, strictly deep, strictly lobar or mixed topography. Covert brain infarcts were detected visually and characterized according to brain topography, imaging characteristics, and size (>3 mm and < 15 mm) [21].

Outcome

At the FHS, non-fasting blood samples collected from each participant in EDTA tubes were immediately centrifuged, aliquoted, and stored at −80°C. Plasma NfL (pg/ml) was analyzed using Quanterix Single Molecule Array (Simoa)TM assay on an HDX analyzer (Quanterix, Billerica, MA). Inter-assay coefficient of variation was 11.73%.

Clinical characteristics

Demographic and clinical characteristics were extracted from the exam cycle closest to MRI as previously described [22]. Systolic and diastolic blood pressures (mmHg) were each taken as the average of the FHS clinic physician's two measurements. We defined hypertension according to JNC-7 (Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) criteria as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mmHg, or use of antihypertensive medications [22]. The values of blood pressure were approximated to the nearest 2 mmHg.

Diabetes mellitus was defined as a fasting blood glucose of ≥126 mg/dL or use of oral hypoglycemic agents or insulin. The values of blood glucose and the lipid panel were approximated to the nearest whole number. We defined current smoking status as self-

reported smoking of at least one cigarette per day within the year preceding examination and use of statins and other medications were also self-reported [22]. *APOE* genotype was defined using previously described methods in the FHS [23]. *APOE* $\varepsilon 4$ carriers included participants with $\varepsilon 2/\varepsilon 4$, $\varepsilon 3/\varepsilon 4$, and $\varepsilon 4/\varepsilon 4$ alleles whereas non-carriers had $\varepsilon 2/\varepsilon 2$, $\varepsilon 2/\varepsilon 3$, or $\varepsilon 3/\varepsilon 3$.

Statistical analysis

Descriptive statistics for clinical and demographic variables were obtained for the overall sample. Plasma NfL concentrations were highly skewed with a mean of 23.6 (±37.4) and median (Q1, Q3) of 17.6 (12.8, 25.5) and were log-transformed for analysis. The log transformed NfL concentrations were normally distributed satisfying the assumptions for linear regression analysis.

Multivariable linear regression analyses were used to relate PVS burden to plasma NfL levels stratified by PVS topography (BG, CSO, and mixed regions). Because of the smaller sample size in some subgroups of PVS burden, we categorized PVS burden in the BG and CSO into high burden (grades III-IV) and low burden (grades I-II) for analysis, with low burden as the reference group. As previously stated, the mixed regions denote high burden neither in the BG nor CSO, high burden strictly in the BG, high burden strictly in the CSO, or concurrent high burden in both brain regions. In the mixed regions, the reference group was no high burden in either the BG or CSO.

Our primary model (model 1) adjusted for age, sex, FHS cohort, time interval between MRI acquisition and clinic examination, and image view (axial or coronal). A second model (model 2) additionally adjusted for hypertension, diabetes mellitus, and smoking. A third model (model 3) included covariates from model 2 and additionally adjusted for CSVD markers: presence of cerebral microbleeds, WMH volume, and covert brain infarcts. Exploratory models adjusted for individual CSVD markers using the covariates from model 2 was done to assess if a particular CSVD marker was driving the attenuation of associations noted. Variance inflation factors were used to assess multicollinearity.

We also evaluated effect measure modification using stratified analyses by age (<65 years, ≥65 years), sex (male, female), presence of hypertension, and *APOE* $\varepsilon 4$ allele presence using the covariates in model 1, removing sex as a covariate in the model assessing effect modification by sex. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). A p value < 0.05 (uncorrected) was considered statistically significant.

RESULTS

The sample comprised of elderly participants with favorable vascular risk factors and fair representation of males and females (Table 1). Participants included in the study were older and had higher proportions of vascular risk factors than those excluded. We observed older age, higher systolic blood pressure, and higher proportion of participants with hypertension as PVS burden increased. Similarly, we observed higher levels of NfL as PVS burden increased both in the BG and CSO regions (Tables 2 and 3). NfL levels were higher in those with high burden strictly in the BG relative to those with strictly high burden in the CSO.

Multivariable analyses (Table 5)

We observed no evidence of multicollinearity in our statistical models (Variance inflation factors < 2 for all variables). In the primary multivariable analyses (model 1), no significant associations were seen between high PVS burden (grade III-IV) in the BG (β = 0.038; 95% CI: −0.033, 0.109; $p = 0.30$) or CSO (β = 0.001; 95% CI: −0.057, 0.059; $p = 0.98$) plasma NfL levels. No considerable changes were noted in subsequent models.

In analyses relating high PVS burden using the mixed regions grouping, we observed that high burden PVS strictly in the BG was significantly associated with plasma NfL in model 1 (β = 0.117; 95% CI: 0.015, 0.219; $p = 0.025$), which remained significant after adjustment for vascular risk factors in model 2 (β = 0.118; 95% CI: 0.014, 0.221; $p = 0.027$). However, the association was attenuated and no longer significant after additional adjustment for other MRI markers of CSVD in model 3 (β = 0.098; 95% CI: −0.041, 0.237; $p = 0.17$).

Exploratory analyses adjusting for markers of CSVD individually in addition to the vascular risk factors in model 2 showed that the association remained significant after adjusting for covert brain infarcts (β = 0.112; 95% CI: 0.067, 0.216; $p = 0.036$), but not when adjusting for WMHV (β = 0.094; 95% CI: −0.016, 0.204; $p = 0.092$) or cerebral microbleeds (β = 0.094; 95% CI: −0.040, 0.227; $p = 0.168$). Lastly, because renal function may influence NfL levels we assessed models adjusting for estimated glomerular filtration rate but did not observe changes in any associations.

Effect modification

We observed that the association of high burden PVS strictly in the BG with higher NfL was modified by age, sex, and *APOE ε*4 allele presence using the covariates in model 1. The associations were significant among women (β = 0.156; 95% CI: 0.024–0.288; $p = 0.021$), participants 65 years and older (β = 0.122; 95% CI: 0.015–0.229; $p = 0.026$), and those without any *APOE ε*4 alleles (β = 0.140; 95% CI: 0.017–0.263; $p = 0.026$; Tables 6–8). In participants < 65 years with high burden PVS in the BG and CSO, there was a borderline association with NfL level though it did not reach statistical significance. In addition, in women only high PVS burden in the BG (which allowed for concurrent high PVS burden in the CSO) was associated with NfL levels (β = 0.101; 95% CI: 0.011–0.191; $p = 0.029$). We did not observe any associations between PVS and NfL level when stratified by presence of hypertension in both the BG (β = 0.256; 95% CI: −0.062–0.113; $p = 0.567$) and CSO (β = 0.115; 95% CI –0.063–0.086; $p = 0.764$). No significant associations between CSO PVS and NfL were observed in any subgroup.

DISCUSSION

In our community-based study of elderly participants free of dementia and stroke, we observed that levels of NfL increased with higher PVS burden. However, in multivariable analyses, only strictly high burden of MRI visible PVS in the BG were related to higher NfL levels compared to those without any high burden of PVS in either region. This association was mainly in women, individuals 65 years or older, and those without any *APOE ε*4 allele.

Most population-based studies examining the association of CSVD with plasma NfL have focused on WMH with paucity of data on MRI visible PVS and NfL. In the Cardiovascular Health Study [6], white matter grade at baseline, and its worsening at follow up, were associated with plasma NfL. Similar findings were noted by Duering and colleagues [3], who observed that WMH and lacunar infarcts were associated with NfL, and in the Swiss atrial fibrillation study, which observed that white matter volumes were associated with higher serum NfL [24]. Our study reports on the novel association of PVS strictly in the BG with plasma NfL, thus expanding previous reports to an additional CSVD marker that may also reflect perivascular drainage impairment.

Although the associations were independent of vascular risk factors, after adjustment for cerebral microbleeds, covert brain infarcts and WMH, they were no longer significant suggesting that the relation of PVS burden with NfL may reflect the same relation as other CSVD markers. Exploratory models individually controlling for cerebral microbleeds, covert brain infarcts, and WMH in addition to vascular risk factors showed that the association was independent of covert brain infarcts but not of WMH volumes or cerebral microbleeds.

From our findings, high burden PVS strictly in the BG was associated with neuroaxonal damage (as reflected by higher NfL levels), which persisted after adjusting for vascular risk factors. If we assume that high PVS burden in the BG reflects the effects of hypertensive arteriopathy, then these results could reflect the effect of hypertension related brain injury. Although our exploratory analyses stratified by history of hypertension did not show different results, the assessment is cross-sectional and does not account for long term trends in hypertension status and blood pressure control. These findings suggest that BG PVS may reflect the same effect of CMB in deep regions which are considered to reflect hypertensive angiopathy. However, MRI visible PVS have also been suggested to reflect impaired perivascular drainage (“glymphatic dysfunction”), which may provide additional insight into the pathophysiology of CSVD and are suggested to be an early marker of CSVD [25].

The different associations noted between the group of high BG PVS burden (which allowed for concurrent high burden in the CSO) and the group of strictly high BG PVS burden (which excluded participants with concurrent high burden in the CSO) could be related to treatment effects or residual confounding. For instance, the proportion of participants with antihypertensive treatment in the highest grade of the high PVS in BG group is 80%, while the proportion on antihypertensive treatment is 63% in the high PVS strictly in BG group. Thus, protective effects from antihypertensive treatment could potentially account for lower NfL levels in the former group.

Although it is important to note that our epidemiological study is cross sectional in nature, which limits causal inferences in the association between PVS and NfL, it may be speculated that exposure to uncontrolled vascular (or other) risk factors leads to high burden of PVS, representing CSVD and glymphatic dysfunction. This in turn may lead to neuronal injury and eventually adverse cognitive outcomes. However, it is possible that once high PVS burden occurs, a vicious cycle ensues where brain and neuronal injury may lead to

further increase in PVS burden through excess production and perivascular accumulation of amyloid-β, for instance.

The subgroup analyses for effect modification noted that the association between strictly high burden PVS in the BG and NfL occurred in those participants 65 years and older and in women, highlighting the strong role of age in neuroaxonal damage and suggesting that sex differences may be important in the relation between brain MRI and some serum markers of neuroaxonal damage. Peters [26] noted different brain regions are affected by aging in both sexes with the frontal and temporal lobes more affected in men while the hippocampus and parietal lobe were more likely affected in women. The borderline association observed in participants younger than 65 years where the group with high PVS burden in both the BG and CSO regions showed a positive association with NfL may suggest that younger individuals < 65 years may experience neuroaxonal damage when diffuse brain involvement occurs, but these finding needs replication. The finding that *APOE ε*4 genotype did not modify the relation of PVS burden with NfL is counterintuitive given the strong association of this genotype with neurodegenerative diseases like Alzheimer's disease, and CSVD such as CAA. Our study, however, cannot exclude a role for *APOE ε*4 alleles in neuroaxonal damage reflected by PVS; given the complexity of genetic and environmental interactions in cerebrovascular disease, it is likely that there are subgroups of individuals where this is true, and our finding may be influenced by residual confounding.

Our study did not find significant associations of high CSO PVS burden with NfL levels. High CSO PVS burden is suggested to represent underlying CAA or advanced hypertensive angiopathy. Although our sample is large, selection of participants was limited by the available measurements, which may have resulted in non-differential selection bias, thus our study cannot exclude that an association is present between PVS in the CSO and NfL. If we assume that they represent advanced hypertensive angiopathy, then it may be that higher hypertension burden (such as longer exposure, exposure to uncontrolled levels) than experienced by the sample studied is needed to reflect higher NfL levels. However, further studies are needed to characterize the relation of CSO PVS with NfL and validate our findings in the BG.

Clinical relevance

NfL is considered a sensitive marker of neuroaxonal damage but is not specific and may be elevated by varied diseases. Our sample included community dwelling individuals free of stroke, dementia and other neurological disorders known to affect brain MRI (such as brain tumors, multiple sclerosis, head injury). We related NfL levels to amyloid-β 40, amyloid-β 42, and plasma tau levels, observing weak but significant correlations suggesting that amyloid and tau related pathways may be implicated (Spearman correlation coefficients 0.077, 0.20, and 0.22, respectively, all $p < 0.01$). Findings from this study, along with reports relating PVS with neuroimaging markers such as lower brain and hippocampal volumes, suggest a role for PVS as marker of ongoing neuronal injury.

Strengths and limitations

Our study has several strengths including its large sample size, evaluation of a plasma NfL in community dwelling individuals free of stroke or dementia, accurate assessment of exposure, outcome and common confounders, and blinded assessments of PVS. The study also has limitations to consider; the sample evaluated is limited by the availability of NfL measurements thus requiring replication in other samples. In terms of selection bias, participants undergoing brain MRI generally tend to be healthier than those in whom MRI is not obtained. We compared the demographic and clinical characteristics between the 1,457 participants included in our sample and the 483 participants excluded. Overall, the samples were similar in age, cohort, sex, and vascular risk factors. NfL levels were also similar with median of 17.6 (IQR:12.8, 25.5) in the included group and 18.3 (IQR: 13.4, 26.2) in the excluded group. Although we cannot entirely exclude selection bias, it would be likely to exclude higher risk individuals, thus biasing results towards null effects.

Although PVS assessments predated NfL measurements, the study is considered cross-sectional in design thus limiting our ability to assess a causal relationship between PVS burden and NfL. We performed multiple comparisons thus our results should be viewed as hypothesis generating and need replication. In addition, the composition of FHS participants which is mainly White European descent limits generalization of findings to other racial groups.

Conclusion

Our findings suggest that high PVS burden strictly in the BG may be associated with higher plasma NfL level suggesting a role for high PVS burden as markers of ongoing neuronal injury. The association is modified by age, sex, and *APOE* genotype highlighting the complexity of relations between neuroimaging and circulating biomarkers. Our findings are hypothesis generating and need replication in other studies.

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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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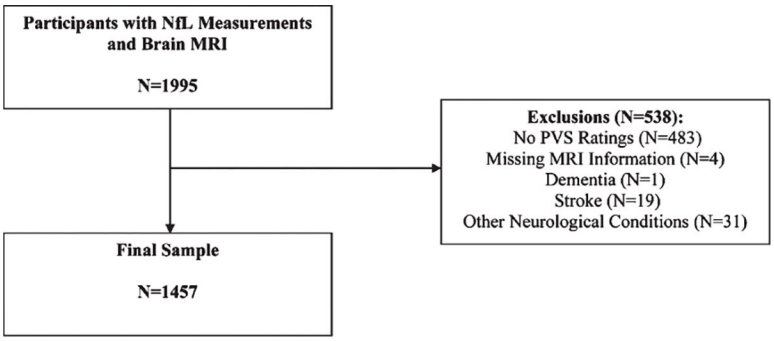

Fig. 1.
Sample Selection.

Table 1

Characteristics of study participants

	Included	Excluded
	N = 1,457	**N = 538**
Clinical Characteristics		
Male, n (%)	655 (45)	254 (47)
Age at exam closest to baseline MRI, y, mean (SD)	68.1 (8.5)	69.5 (8.6)
Age at MRI, y, mean (SD)	70.1 (8.5)	69.1 (9.9)
*APOE ε*4+, n (%)	327 (23)	110 (20)
FHS Cohort, n (%)		
Offspring	1325 (91)	448 (83)
OMNI 1	132 (9)	90 (17)
Time between biomarker measurement and MRI, y, mean (SD)	1.4 (1.0)	1.4 (1.1)
Vascular Risk Factors		
Systolic blood pressure, mmHg, mean (SD)	126.0 (16.0)	126.0 (18.0)
Diastolic blood pressure, mmHg, mean (SD)	72.0 (10.0)	72.0 (10.0)
Total cholesterol, mg/dl, mean (SD)	187.0 (36.8)	182.6 (41.1)
High density lipoprotein, mg/dl, mean (SD)	61.0 (18.6)	60.9 (20.5)
Low density lipoprotein, mg/dl, mean (SD)	103.4 (31.2)	98.5 (33.1)
Triglycerides, mg/dl, mean (SD)	114.0 (57.3)	116.2 (59.3)
Fasting blood glucose, mg/dl, mean (SD)	103.0 (20.2)	103.9 (20.6)
N = 1,428		
Hypertension[a], n (%)	835 (57)	254 (47)
Current smoker, n (%)	85 (6)	40 (7)
Diabetes mellitus, n (%); N = 1,407	213 (15)	92 (18)
Antihypertensive use, n (%)	717 (49)	316 (59)
Lipid lowering medication use, n (%)	669 (46)	276 (52)
Body mass index, kg/m^2, mean (SD)	28.1 (5.2)	28.3 (5.3)
Basal ganglia PVS, n (%)		
Grade I	564 (39)	–

J Alzheimers Dis. Author manuscript; available in PMC 2024 August 05.

	Included	Excluded
	N = 1,457	**N = 538**
Grade II	672 (46)	–
Grade III	191 (13)	–
Grade IV	30 (2)	–
Centrum semiovale PVS, n (%)		
Grade I	376 (26)	–
Grade II	716 (49)	–
Grade III	301 (21)	–
Grade IV	64 (4)	–
High Burden PVS[b], n (%)		
None	1,000 (69)	–
Basal ganglia only	92 (6)	–
Centrum semiovale only	236 (16)	–
Basal ganglia & centrum semiovale	129 (9)	–
Neurofilament light chain, (pg/ml) median (25^{th}; 75^{th} percentile)	17.6 (12.8, 25.5)	18.3 (13.4, 25.8)
White matter hyperintensities[c], mean (SD); N = 1,323	0.0 (1.0)	–
Cerebral microbleed, n (%); N = 948	97 (10)	–
Covert brain infarct, n (%)	125 (9)	–

FHS, Framingham Heart Study; MRI, magnetic resonance imaging; PVS, perivascular spaces; SD, standard deviation.

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

[b] High burden PVS is defined as grade III-IV in the respective region(s).

[c] Log white matter hyperintensity volume standardized to mean 0 and standard deviation of 1.

J Alzheimers Dis. Author manuscript; available in PMC 2024 August 05.

Table 2

Characteristics of participants by PVS topography – Basal ganglia

	Basal Ganglia PVS			
Clinical characteristics	**Grade I N = 564**	**Grade II N = 672**	**Grade III N = 191**	**Grade IV N = 30**
Male, n (%)	274 (49)	287 (43)	83 (43)	11 (37)
Age at exam closet to baseline MRI, y, mean (SD)	64.1 (8.2)	69.6 (7.6)	73.2 (6.9)	79.1 (6.1)
Age at MRI, y, mean (SD)	66.0 (8.2)	71.5 (7.6)	75.1 (6.9)	81.1 (5.6)
Time between biomarker measurement and MRI, y, mean (SD)	1.4 (1)	1.5 (1.0)	1.4 (1.0)	1.5 (1.0)
*APOE ε*4, n (%); N = 1,414	118 (21)	157 (24)	45 (25)	7 (24)
FHS Cohort, n (%)				
Offspring	494 (88)	622 (93)	180 (94)	29 (97)
OMNI 1	70 (12)	50 (7)	11 (6)	1 (3)
Vascular risk factors				
Systolic blood pressure, mmHg, mean (SD)	124.0 (16.0)	126.0 (16.0)	132.0 (18.0)	132.0 (16.0)
Diastolic blood pressure, mmHg, mean (SD)	74.0 (10.0)	72.0 (10.0)	72.0 (10.0)	68.0 (12.0)
Total cholesterol, mg/dl, mean (SD)	189 (37.0)	186 (37.0)	186 (37.0)	178.0 (34.0)
High density lipoprotein, mg/dl, mean (SD)	60.0 (19.0)	61.0 (18.0)	64.0 (21.0)	61.0 (19.0)
Low density lipoprotein, mg/dl, mean (SD)	106.0 (32.0)	102.0 (31.0)	100.0 (31.0)	93.0 (26.0)
Triglyceride, mg/dl, mean (SD)	114.0 (57.0)	114.0 (57.0)	115.0 (60.0)	115.0 (65.0)
Fasting blood glucose, mg/dl, mean (SD)	102.0 (20.0)	104.0 (21.0)	102.0 (17.0)	107.0 (20.0)
Hypertension[a] n (%)	271 (48)	405 (60)	134 (70)	25 (83)
Current smoker, n (%)	31 (6)	48 (7)	5 (3)	1 (3)
Diabetes mellitus, n (%)	69 (13)	111 (17)	27 (14)	6 (21)
Antihypertensive use, n (%)	224 (40)	351 (52)	118 (62)	24 (80)
Lipid lowering medication use, n (%)	219 (39)	322 (48)	108 (57)	20 (67)
Body mass index, kg/m^2, mean (SD)	28.2 (5.1)	28.2 (5.3)	27.9 (5.1)	26.8 (5.1)
Neurofilament light chain, (pg/ml), median (25th; 75th percentile)	15.2 (11.6, 21.4)	18.1 (13.4, 26.5)	23.1 (16.0, 29.8)	27.5 (22.3, 32.5)
White matter hyperintensities[b], mean (SD); N = 1,323	−0.4 (0.9)	0 (0.9)	0.6 (0.8)	1.2 (0.9)
Cerebral microbleed, n (%); N = 948	34 (9)	39 (9)	20 (17)	4 (21)
Covert brain infarct, n (%)	27 (5)	55 (8)	35 (18)	8 (27)

FHS, Framingham Heart Study; MRI, magnetic resonance imaging; PVS, perivascular spaces; SD, standard deviation.

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

[b] Log white matter hyperintensity volume standardized to mean 0 and standard deviation of 1.

Table 3

Characteristics of study participants by PVS topography – Centrum Semiovale

	Centrum Semiovale PVS			
Clinical characteristics	**Grade I** **N = 376**	**Grade II** **N = 716**	**Grade III** **N = 301**	**Grade IV** **N = 64**
Male, n (%)	186 (49)	320 (45)	123 (41)	26 (41)
Age at exam closet to baseline MRI, y, mean (SD)	64.2 (8.5)	68.4 (8.2)	71.1 (7.5)	73.0 (7.7)
Age at MRI, y, mean (SD)	66.1 (8.5)	70.4 (8.2)	73.1 (7.4)	74.9 (7.9)
Time between biomarker measurement and MRI, y, mean (SD)	1.4 (1.1)	1.5 (1.0)	1.5 (1.0)	1.4 (1.0)
*APOE ε*4, n (%); N = 1,414	93 (25)	137 (20)	80 (28)	17 (27)
FHS Cohort, n (%)				
Offspring	329 (88)	651 (91)	283 (94)	62 (97)
OMNI 1	47 (13)	65 (9)	18 (6)	2 (3)
Vascular risk factors				
Systolic blood pressure, mmHg, mean (SD)	122.0 (14.0)	126.0 (16.0)	128.0 (18.0)	132.0 (16.0)
Diastolic blood pressure, mmHg, mean (SD)	74.0 (10.0)	72.0 (10.0)	72.0 (10)	72.0 (12.0)
Total cholesterol, mg/dl, mean (SD)	190.0 (35.0)	185.0 (38.0)	188.0 (36.0)	187.0 (38.0)
High density lipoprotein, mg/dl, mean (SD)	60.0 (19.0)	61.0 (18.0)	63.0 (19.0)	64.0 (19.0)
Low density lipoprotein, mg/dl, mean (SD)	10.08 (30.0)	102.0 (32.0)	101.0 (30.0)	102.0 (29.0)
Triglyceride, mg/dl, mean (SD)	116.0 (64.0)	112.0 (55.0)	117.0 (57.0)	105.0 (51.0)
Fasting blood glucose, mg/dl, mean (SD)	102.0 (22.0)	103.0 (20.0)	102.0 (20.0)	102.0 (19.0)
Hypertension[a], n (%)	167 (44)	428 (60)	193 (64)	47 (73)
Current smoker, n (%)	21 (6)	45 (6)	14 (5)	5 (8)
Diabetes mellitus, n (%)	51 (14)	104 (15)	50 (17)	8 (13)
Antihypertensive use, n (%)	149 (40)	363 (51)	165 (55)	40 (63)
Lipid lowering medication use, n (%)	159 (42)	330 (46)	147 (49)	33 (52)
Body mass index, kg/m^2, mean (SD)	28.2 (5.1)	28.4 (5.3)	27.6 (4.9)	27.5 (5.5)
Neurofilament light chain, (pg/ml), median (25th; 75th percentile)	15.2 (11.6, 20.2)	17.5 (12.8, 26.8)	21.1 (14.4, 28.8)	23.4 (16.5, 30.8)
White matter hyperintensities[b], mean (SD); N = 1,323	−0.5 (0.9)	−0.1 (0.9)	0.5 (1)	0.6 (0.8)
Cerebral microbleed, n (%); N = 948	18 (7)	47 (10)	27 (13)	5 (11)

J Alzheimers Dis. Author manuscript; available in PMC 2024 August 05.

	Centrum Semiovale PVS			
Clinical characteristics	**Grade I**	**Grade II**	**Grade III**	**Grade IV**
	N = 376	**N = 716**	**N = 301**	**N = 64**
Covert brain infarct, n (%)	9 (2)	71 (10)	35 (12)	10 (16)

FHS, Framingham Heart Study; MRI, magnetic resonance imaging; PVS, perivascular spaces; SD, standard deviation.

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

[b] Log white matter hyperintensity volume standardized to mean 0 and standard deviation of 1.

Table 4

Characteristics by mixed region high burden PVS

	Mixed Region High Burden PVS[a]			
Clinical characteristics	**None N = 1,000**	**Basal Ganglia Only N = 92**	**Centrum Semiovale Only N = 236**	**Basal Ganglia & Centrum Semiovale N = 129**
Male, n (%)	466 (47)	40 (43)	95 (40)	54 (42)
Age at exam closet to baseline MRI, y, mean (SD)	66.4 (8.4)	73.3 (7.5)	69.8 (7.4)	74.5 (6.7)
Age at MRI, y, mean (SD)	68.4 (8.4)	75.1 (7.5)	71.7 (7.4)	76.5 (6.7)
Time between biomarker measurement and MRI, y, mean (SD)	1.5 (1.0)	1.4 (0.9)	1.5 (1.0)	1.5 (1.1)
APOE ε4, n (%); N = 1,414	211 (22)	19 (22)	64 (28)	33 (27)
FHS Cohort, n (%)				
Offspring	897 (90)	83 (90)	219 (93)	126 (98)
OMNI 1	103 (10)	9 (10)	17 (7)	3 (2)
Vascular risk factors				
Systolic blood pressure, mmHg, mean (SD)	126.0 (16.0)	130.0 (16.0)	126.0 (18.0)	134.0 (18.0)
Diastolic blood pressure, mmHg, mean (SD)	74.0 (10.0)	72.0 (10.0)	72.0 (10.0)	70.0 (10.0)
Total cholesterol, mg/dl, mean (SD)	188.0 (37.0)	176.0 (34.0)	186.0 (36.0)	191.0 (37.0)
High density lipoprotein, mg/dl, mean (SD)	60.0 (18.0)	61.0 (21.0)	62.0 (19.0)	65.0 (19.0)
Low density lipoprotein, mg/dl, mean (SD)	105.0 (32.0)	92.0 (27.0)	100.0 (29.0)	103.0 (31.0)
Triglyceride, mg/dl, mean (SD)	113.0 (57.0)	116.0 (69.0)	116.0 (57.0)	115.0 (54.0)
Fasting blood glucose, mg/dl, mean (SD)	103.0 (21.0)	102.0 (17.0)	102.0 (20.0)	103.0 (18.0)
Hypertension[b], n (%)	533 (53)	62 (67)	143 (61)	97 (75)
Current smoker, n (%)	64 (6)	2 (2)	15 (6)	4 (3)
Diabetes mellitus, n (%)	141 (15)	14 (15)	39 (17)	19 (15)
Antihypertensive use, n (%)	454 (45)	58 (63)	121 (51)	84 (65)
Lipid lowering medication use, n (%)	428 (43)	61 (66)	113 (48)	67 (52)
Body mass index, kg/m^2, mean (SD)	28.4 (5.2)	27.9 (4.9)	27.6 (4.9)	27.6 (5.3)
Neurofilament light chain, (pg/ml), median (25th; 75th percentile)	16.3 (12.2, 22.9)	22.5 (15.4, 35.6)	19.1 (14.0, 28.6)	24.0 (18.1, 29.1)
White matter hyperintensities[c], mean (SD); N = 1323	−0.3 (0.9)	0.5 (0.9)	0.3 (0.9)	0.9 (0.8)
Cerebral microbleed, n (%); N = 948	59 (9)	6 (11)	14 (9)	18 (21)

J Alzheimers Dis. Author manuscript; available in PMC 2024 August 05.

	Mixed Region High Burden PVS[a]			
Clinical characteristics	**None N = 1,000**	**Basal Ganglia Only N = 92**	**Centrum Semiovale Only N = 236**	**Basal Ganglia & Centrum Semiovale N = 129**
Covert brain infarct, n (%)	63 (6)	17 (18)	19 (8)	26 (20)

FHS, Framingham Heart Study; MRI, magnetic resonance imaging; PVS, perivascular spaces; SD, standard deviation.

[a] High burden PVS is defined as grade III-IV in the respective region.

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

[c] Log white matter hyperintensity volume standardized to mean 0 and standard deviation of 1.

Table 5

Multivariable analysis of the association of PVS with neurofilament light chain

	Model 1		Model 2		Model 3	
	β (95% CI)	***p***	**β (95% CI)**	***p***	**β (95% CI)**	***p***
Basal Ganglia						
Grade I-II	REF		REF		REF	
Grade III-IV	0.038 (−0.033, 0.109)	0.290	0.038 (−0.033, 0.110)	0.294	0.010 (−0.085, 0.105)	0.832
Centrum Semiovale						
Grade I-II	REF		REF		REF	
Grade III-IV	0.001 (−0.057, 0.059)	0.973	0.003 (−0.056, 0.062)	0.914	−0.004 (−0.080, 0.073)	0.926
Mixed Region High PVS Burden *						
None	REF		REF		REF	
Basal ganglia only	0.117 (0.015, 0.219)	0.025	0.117 (0.014, 0.221)	0.027	0.098 (−0.041, 0.237)	0.168
Centrum semiovale only	0.025 (−0.042, 0.093)	0.462	0.029 (−0.04, 0.098)	0.416	0.029 (−0.059, 0.118)	0.518
Centrum semiovale and Basal ganglia	−0.009 (−0.099, 0.081)	0.838	−0.009 (−0.101, 0.083)	0.853	−0.034 (−0.153, 0.086)	0.582

CI, confidence interval; FHS, Framingham Heart Study; MRI, magnetic resonance imaging; PVS, perivascular spaces. Model 1: adjusted for age, sex, FHS cohort, time interval between MRI and clinic visits and image type (axial or coronal). Model 2: additionally adjusted for hypertension, diabetes, smoking. Model 3: adjusted model 2 and additionally for cerebral microbleeds, covert brain infarcts, and white matter hyperintensities.

*High PVS burden is defined as grades III-IV PVS in the respective region(s).

Table 6

Multivariable regression analysis of high burden (>20 counts) PVS in the basal ganglia, centrum semiovale, and mixed regions stratified by age

	Age < 65 (*n* = 386)		Age 65+ (*n* = 1,071)	
	β (95% CI)	***p***	**β (95% CI)**	***p***
Basal Ganglia				
Grade I-II	REF		REF	
Grade III-IV	0.168 (−0.151, 0.486)	0.301	0.025 (−0.048, 0.099)	0.500
Centrum Semiovale				
Grade I-II	REF		REF	
Grade III-IV	−0.002 (−0.155, 0.150)	0.975	−0.001 (−0.064, 0.063)	0.985
Mixed Region High PVS Burden *				
None	REF		REF	
Basal ganglia only	−0.024 (−0.424, 0.377)	0.907	0.122 (0.015, 0.229)	**0.026**
Centrum semiovale only	−0.043 (−0.200, 0.115)	0.594	0.040 (−0.036, 0.115)	0.306
Centrum semiovale and Basal ganglia	0.477 (−0.040, 0.993)	0.071	−0.027 (−0.120, 0.066)	0.572

CI, confidence interval; FHS, Framingham Heart Study; MRI, magnetic resonance imaging; PVS, perivascular spaces. Models adjusted for age, sex, FHS cohort, time interval between MRI and clinic exam, image type (axial or coronal).

*High PVS burden is defined as grades III-IV PVS in the respective region(s).

Table 7

Multivariable regression analysis of high burden (>20 counts) PVS in the basal ganglia, centrum semiovale, and mixed regions stratified by sex

	Female (*n* = 802)		Male (*n* = 655)	
	β (95% CI)	***p***	**β (95% CI)**	***p***
Basal Ganglia				
Grade I-II	REF		REF	
Grade III-IV	0.101 (0.011, 0.191)	0.029	−0.042 (−0.154, 0.069)	0.456
Centrum Semiovale				
Grade I-II	REF		REF	
Grade III-IV	0.022 (−0.053, 0.096)	0.569	−0.024 (−0.116, 0.067)	0.602
Mixed Region High PVS Burden *				
None	REF		REF	
Basal ganglia only	0.156 (0.024, 0.288)	**0.021**	0.071 (−0.090, 0.231)	0.388
Centrum semiovale only	0.023 (−0.063, 0.109)	0.602	0.035 (−0.073, 0.143)	0.528
Centrum semiovale and Basal ganglia	0.072 (−0.044, 0.187)	0.225	−0.115 (−0.257, 0.028)	0.114

CI, confidence interval; FHS, Framingham Heart Study; MRI, magnetic resonance imaging; PVS, perivascular spaces. Models adjusted for age, sex, FHS cohort, time interval between MRI and clinic exam, image type (axial or coronal).

* High PVS burden is defined as grades III-IV PVS in the respective region(s).

Table 8

Multivariable regression analysis of high burden (>20 counts) PVS in the basal ganglia, centrum semiovale, and mixed regions stratified by presence or absence of *APOE ε*4

	***APOE ε*4 Absent (*n* = 1,087)**		***APOE ε*4 Present (*n* = 327)**	
	β (95% CI)	***p***	**β (95% CI)**	***p***
Basal Ganglia				
Grade I-II	REF		REF	
Grade III-IV	0.051 (−0.035, 0.137)	0.246	0.029 (−0.100, 0.158)	0.659
Centrum Semiovale				
Grade I-II	REF		REF	
Grade III-IV	0.012 (−0.060, 0.083)	0.745	−0.043 (−0.144, 0.059)	0.410
Mixed Region High PVS Burden *				
None	REF		REF	
Basal ganglia only	0.140 (0.017, 0.263)	**0.026**	0.058 (−0.141, 0.258)	0.567
Centrum semiovale only	0.042 (−0.042, 0.126)	0.326	−0.049 (−0.167, 0.070)	0.419
Centrum semiovale and Basal ganglia	−0.002 (−0.113, 0.110)	0.976	−0.010 (−0.170, 0.149)	0.897

CI, confidence interval; FHS, Framingham Heart Study; MRI, magnetic resonance imaging; PVS, perivascular spaces. Models adjusted for age, sex, FHS cohort, time interval between MRI and clinic exam, image type (axial or coronal).

*High PVS burden is defined as grades III-IV PVS in the respective region(s).