### Title

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# Enlarged perivascular spaces and plasma Aβ42/Aβ40 ratio in older adults without dementia

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## Abstract

Dilation of perivascular spaces (PVS) in the brain may indicate poor fluid drainage due to accumulation of perivascular cell debris, waste, and proteins, including amyloid-beta (Aβ). No prior study has assessed whether plasma Aβ levels are related to PVS in older adults without dementia. Independently living older adults (N = 56, mean age = 68.2 years; SD = 6.5; 30.4% male) free of dementia or clinical stroke were recruited from the community and underwent brain MRI, and venipuncture. PVS were qualitatively scored and dichotomized to low PVS burden (scores 0–1,) or high PVS burden (score >1). Plasma was assayed using a Quanterix Simoa®> Kit to quantify Aβ42 and Aβ40 levels. A significant difference was observed in plasma Aβ42/Aβ40 ratio between low and high PVS burden, controlling for age ($F(1,53) = 5.59$ $p = 0.022$, $\eta 2 = .10$), with lower Aβ42/Aβ40 ratio in the high PVS burden group. Dilation of PVS is associated with lower plasma Aβ42/Aβ40 ratio, which may indicate higher cortical amyloid deposition. Future longitudinal studies examining PVS changes, and the pathogenesis of AD are warranted.

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Author Contributions

**Daniel A Nation**: Conceptualization, Methodology, Formal Analysis, Writing - Review & Editing, Supervision; **Arunima Kapoor**: Formal Analysis, Investigation, Data Curation, Writing - Original Draft. **All Co-Authors**: Investigation, Data Curation, Writing - Review & Editing.

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**Keywords**

Aβ42/Aβ40 Ratio; Alzheimer's Disease; Perivascular Spaces; Small Vessel Disease; Vascular Cognitive Impairment

Perivascular spaces (PVS) are part of the brain's glymphatic system, which enables movement and distribution of substances, and clearance of metabolic waste and proteins (Bakker et al., 2016; Plog and Nedergaard, 2018; Wardlaw et al., 2020). Dilation of this PVS is a feature of small vessel disease and represents underlying damage to the cerebral vasculature (Doubal et al., 2010). Enlarged PVS are associated with aging, cognitive impairment, Alzheimer's disease (AD), depression and multiple sclerosis, among other conditions (Francis et al., 2019; Wardlaw et al., 2020). While the precise mechanism of waste clearance in the brain is still under investigation, dilation of PVS may indicate poor cerebral fluid drainage due to accumulation of perivascular cell debris and proteins, including amyloid-beta (Aβ) and other toxic waste products (Bakker et al., 2016; Keable et al., 2016; Roher et al., 2003).

Aβ deposition is currently considered a hallmark and key pathophysiological marker of AD (Jack et al., 2018). The amyloid cascade hypothesis posits that aggregation of Aβ in the brain impairs synaptic function, damaging neurons and leading to neurodegeneration, cognitive impairment and ultimately dementia (Hardy and Selkoe, 2002; Hardy and Higgins, 1992). The causal role of Aβ deposition has since been called into question by evidence from failed clinical trials indicating clearance of Aβ does not lead to robust or reproducible cognitive benefits (Knopman et al., 2021). Nevertheless, Aβ biomarkers remain important hallmarks of AD pathophysiology regardless of their status as a treatment target. Currently, Aβ can be measured in the brain parenchyma using amyloid positron emission tomography (PET), as well as in cerebrospinal fluid (CSF) and blood using biochemical assays (Blennow et al., 2015a; Hansson et al., 2019a; Herholz and Ebmeier, 2011). Amyloid PET and CSF sample collection are both relatively invasive procedures, requiring injection of a radiotracer and lumbar puncture, respectively (Blennow et al., 2015b). However, novel specific and sensitive assays now allow Aβ to be measured in plasma (Blennow, 2017). Low plasma Aβ42/Aβ40 ratio is associated with higher cortical amyloid deposition (Fandos et al., 2017a) and risk of developing AD, making it a valuable biomarker (Doecke et al., 2020a; Graff-Radford et al., 2007; van Oijen et al., 2006a).

Few prior studies have examined whether plasma Aβ levels may be associated with enlarged PVS. Enlarged PVS have been linked to vascular Aβ deposition in cerebral amyloid angiopathy (CAA) based on neuropathological examination of the brain (Perosa et al., 2022a). Similarly, in patients with Alzheimer's disease–related cognitive impairment, enlarged PVS in the centrum semiovale are associated with Aβ positivity using amyloid PET imaging (Kim et al., 2021). One previous study has also observed a relationship between CSF biomarkers of AD and enlargement of PVS in a sample of amyloid positive cognitively normal individuals on the AD continuum (Vilor-Tejedor et al., 2021a). Yet, to the best of our knowledge, no prior study has assessed whether lower plasma Aβ levels are related to enlarged PVS in healthy older adults.

The current study examined whether plasma Aβ levels differ between older adults with higher number of enlarged PVS visible on MRI compared to those with no or minimal enlarged PVS burden. We hypothesized that plasma Aβ levels will be lower in individuals with higher burden of enlarged PVS.

## Methods

### Participants

Participants were recruited from the community and all study procedures were conducted at the Vascular Senescence and Cognition (VaSC) Study at the University of Southern California (USC) and University of California, Irvine (UCI). Older adults aged 55 years or older who were living independently were included. Exclusion criteria included history of clinical stroke, dementia, myocardial infarction, major neurological or psychiatric disorder impacting cognition, MRI contraindication, current organ failure, and other systemic or neurological illness that may impact central nervous system function. History of vascular risk factors, including hypertension, body mass index, dyslipidemia, diabetes, as well as history of other medical illnesses, was determined by clinical interview. This study was approved by the University of Southern California and University of California, Irvine Institutional Review Board. All participants gave informed consent and underwent detailed clinical assessment to determine demographics and medical history, blood draw for quantification of Aβ levels and brain MRI for quantification of PVS. All participants also underwent comprehensive neuropsychological assessment evaluating multiple cognitive domains. Results of cognitive testing were reviewed by two, blinded neuropsychologists (JJ, DN) and all participants were determined to be free of dementia by clinical consensus conference.

### Neuroimaging

All participants at both study sites underwent a brain MRI on a Siemens 3T Prisma scanner using identical protocols. The following sequences were examined for the current analysis: 3D T1-weighted anatomical scan for qualitative assessment of brain structures and abnormalities (Scan parameters: TR = 2300 ms; TE = 2.98 ms; TI = 900 ms; flip angle = 9 deg; resolution = 1.0 × 1.0 × 1.2 $mm^3$), T2-weighted scan for identification of enlarged PVS (Scan parameters: TR = 10000 ms; TE = 88.0 ms; flip angle = 120 deg; resolution = 0.8 × 0.8 × 3.5 $mm^3$) and FLAIR (Scan parameters: TR = 10000 ms; TE = 91.0 ms; flip angle = 150 deg; resolution = 0.9 × 0.9 × 5.0 $mm^3$) for differentiation of PVS in the context of white matter hyperintensities.

**Perivascular Spaces—**PVS were identified in accordance with established neuroimaging standards for SVD (Smith et al., 2019) and scored using the *Enlarged Perivascular Spaces (EPVS): A Visual Rating Scale and User Guide* developed by Potter, Morris & Wardlaw (2015). (Potter et al., 2015). PVS were scored by a blinded doctoral candidate (AK) who was trained by a board-certified neuroradiologist and has 6 years of experience scoring small vessel disease. The basal ganglia, centrum semiovale, and midbrain were examined. For the basal ganglia and centrum semiovale, at least 3 slices were reviewed in the locations as described in the scoring guide. The slice with the highest PVS count was recorded. Both

hemispheres of the brain were reviewed but only the highest number from one side was scored. All images were scored on the axial orientation. Overall PVS score was the score of anatomical region with the highest score. Scores ranged from 0 (no enlarged PVS) to 4 (>40 enlarged PVS, severe) and were dichotomized to low enlarged PVS burden (scores of 0–1, none or mild) or high enlarged PVS burden (score >1, moderate-severe). White matter hyperintensities were qualitatively scored using the Fazekas scale on the FLAIR sequence.

### Venipuncture

Venipuncture was performed after an overnight 12-hour fast. Blood was drawn into 6 mL $K_3$EDTA-coated tubes. Plasma was separated by density gradient centrifugation at 1000 × g for 10 minutes at room temperature. Plasma was aliquoted into cryovials and stored at −80 °C until the assay was conducted.

### Aβ Quantification

Plasma levels of Aβ40 and Aβ42 were determined and Aβ42/Aβ40 ratio was calculated. Aβ40 and Aβ42 were processed using the digital immunoassay, Simoa®> Neurology 3-Plex A (N3PA) Advantage Kit (Quanterix), following the manufacturer's protocol. Accepted ranges were as follows: $A\beta_{1–40}$ = 0 – 560 pg/mL and $A\beta_{1–42}$ = 0 – 240 pg/mL.

### Statistical Analyses

All analyses were performed using IBM SPSS Statistics 27, R Version 3.6.1 and GraphPad Prism version 8.0.0. Demographic variables were computed to characterize the sample. One-way ANCOVA was conducted to compare Aβ40, Aβ42, Aβ42/Aβ40 ratio between low and high enlarged PVS burden controlling for age. Significance threshold was set at $p < .05$. No prior studies were available to conduct a sample size calculation, however, based on a sensitivity power analysis, our sample size with 80% power and $\alpha = .05$ was sufficient to detect a medium-large effect size.

## Results

A total of 56 participants were included in the current analysis. Age of study participants ranged from 55 to 84 years (Median = 68, Interquartile Range (IQR) = 12) and years of education ranged from 9 to 20 (Median = 16, IQR = 2). Participant characteristics are reported in Table I. Thirty-nine (69.6%) had high overall burden (Figure I), 37 (66.1%) participants had high burden of enlarged PVS in the centrum semiovale, and 17 (30.4%) had high burden in the basal ganglia. Majority (N = 52, 92.9%) had enlarged PVS in the midbrain. No differences in demographic factors were observed between those with high versus low burden of enlarged PVS (Table 1). Based on detailed neuropsychological assessment, none of the participants met criteria for dementia and 9met criteria for mild cognitive impairment, which did not differ by PVS burden (p = .562).

### Aβ Levels in Low and High Enlarged PVS Burden

There was a significant difference in plasma Aβ42/Aβ40 ratio between low and high overall PVS burden (Figure I), controlling for age ($F(1,53) = 5.59$ $p = 0.022$, $\eta^2 = .10$), with lower Aβ42/Aβ40 ratio in high PVS burden group (estimated marginal mean = .050) compared to

the low PVS burden group (estimated marginal mean = .062). This difference was driven primarily by enlarged PVS in the centrum semiovale ($F(1,53) = 6.07$ $p = 0.017$, $\eta^2 = .10$). No difference in plasma Aβ42/Aβ40 ratio was observed between low versus high PVS burden in the basal ganglia ($F(1,53) = 0.02$, $p = 0.898$).

No difference was observed in Aβ42 or Aβ40 levels between groups, although the difference in Aβ42 levels between low and high overall burden of PVS was approaching significance ($F(1,53) = 3.65$ $p = 0.064$, $\eta^2 = .06$, Figure I).

A correlation analysis between PVS score and Aβ42/40 ratio yielded similar results: PVS score in the centrum semiovale was associated with Aβ42/40 ratio ($r = -.281$, $p = .036$, $N = 56$) while PVS score in the basal ganglia was not associated with Aβ42/40 ratio ($r = -.076$, $p = .577$, $N = 56$)

We conducted additional analyses including MCI diagnosis in our model, which yielded the same results. There was significantly lower plasma Aβ42/Aβ40 ratio in older adults with higher overall PVS burden relative to those with lower PVS burden, controlling for age and diagnosis ($F(1, 52) = 5.03$ $p = 0.029$, $\eta2 = .09$). Similarly, this lower plasma Aβ42/Aβ40 ratio was primarily observed in those with enlarged PVS specifically in the centrum semiovale ($F(1, 52) = 5.20$ $p = 0.027$, $\eta2 = .09$). No difference in plasma Aβ42/Aβ40 ratio was observed between low versus high PVS burden in the basal ganglia after adjusting for age and diagnosis ($F(1, 52) = 0.00$, $p = 0.997$).

## Discussion

Aβ deposition is a key feature of AD and recent advances in blood-based fluid biomarkers have allowed detection of Aβ40 and Aβ42 levels in plasma (Doecke et al., 2020b; Jack et al., 2018; van Oijen et al., 2006b). Prior studies have hypothesized that elimination of Aβ from the brain occurs via perivascular spaces and that failure to eliminate Aβ may contribute to the pathogenesis of AD (Preston et al., 2003a; Roher et al., 2003b). To the best of our knowledge, this is the first study to demonstrate that lower plasma Aβ42/Aβ40 ratio is associated with greater dilation of PVS in the brain.

CSF concentration of Aβ42 is a crucial biomarker for AD diagnosis, however the ratio of Aβ42 to Aβ40 is more valuable in diagnosing AD (Hansson et al., 2019b). Similarly, lower plasma Aβ42/Aβ40 ratio is indicative of greater Aβ deposition and is able to predict amyloid-PET positivity and risk of AD (Doecke et al., 2020b; Pérez-Grijalba et al., 2018). Accumulation of Aβ in the cortex or cerebral vessels could impair drainage of interstitial fluid leading to enlarged PVS (Preston et al., 2003b). Higher burden of enlarged PVS in the centrum semiovale has previously been reported in amyloid-PET positive individuals with AD-related cognitive impairment (Kim et al., 2021), however findings have been inconsistent (Banerjee et al., 2017; Wang et al., 2021). One post-mortem study, however, found that greater cerebrovascular amyloid deposition was associated with enlarged perivascular spaces (Perosa et al., 2022b).

Our findings are consistent with these prior studies, demonstrating that lower levels of amyloid circulating in blood—and therefore greater deposition of amyloid in the brain

(Fandos et al., 2017b)—is associated with dilation of the PVS. Our findings are also consistent with the literature showing enlargement of PVS in the centrum semiovale specifically may be associated with Aβ pathologies (Charidimou et al., 2015), while enlargement in the basal ganglia may instead be more indicative of arteriolosclerosis and hypertensive arteriopathy (Vilor-Tejedor et al., 2021b). Given the role of PVS in the centrum semiovale in CAA as defined by the Boston criteria version 2.0 (Charidimou et al., 2022), our observation of a greater association of Aβ42/40 with PVS in the centrum semiovale could indicate presence of CAA. However, additional studies—particularly those employing longitudinal designs— are needed to further determine the association of PVS in the basal ganglia and centrum semiovale to arteriolosclerosis and Aβ pathologies.

These findings also lend support to the use of plasma Aβ42/Aβ40 ratio as valuable marker of not only AD-related changes in the brain but also changes in the cerebral microvasculature (Gurol et al., 2006). Prior studies have observed an association between amyloid in plasma specifically and other cerebrovascular pathology, such as white matter hyperintensities (Janelidze et al., 2016a). Plasma amyloid is known to affect endothelial cell function, and vascular changes such as chronic cerebral hypoperfusion may stimulate production of Aβ, specifically in circulation (Bennett et al., 2000; Janelidze et al., 2016b; Paris et al., 2003). Therefore, it remains unclear whether plasma levels of Aβ may be more closely related to cerebrovascular pathology compared to other methods of assessing Aβ, such as using PET or CSF.

One limitation of this study is the cross-sectional study design and does not provide insight into causality or directionality. It is possible that PVS dilation is secondary to Aβ deposition, or that Aβ deposition occurs due to other processes that are also associated with PVS dilation. Longitudinal studies are warranted to determine causality and directionality as well as examine any moderating or mediating factors that could influence this relation. Future studies could elucidate whether Aβ deposition may be a cause or consequence of PVS dilation. However, given that our sample includes older adults free of stroke and dementia, our findings suggest that plasma Aβ42/Aβ40 ratio could be altered prior to the development of cognitive impairment and could serve as pre-clinical marker. Moreover, plasma levels of Aβ42 and Aβ40 can be obtained non-invasively, while current methods of determining amyloid levels require invasive procedure (Hansson et al., 2019b). Another limitation of this study is that amyloid is also produced and metabolized peripherally and therefore concentrations may be impacted by cerebral and peripheral factors (Janelidze et al., 2016b; Roher et al., 2009). Despite this, we observed an association between plasma levels of Aβ and microvascular changes visible on brain MRI, which suggests that plasma levels of Aβ may be related to cerebrovascular changes. While this study utilized qualitative visual rating of PVS, future studies could use PVS volumetry, which may allow greater granularity and variability. Pipelines to quantify PVS volumes are currently being developed (Ballerini et al., 2020; Sepehrband et al., 2019; Spijkerman et al., 2022) and this study can be further validated using such methods. Moreover, while our sample in this study consisted primarily of healthy older adults, future studies should also examine this association in individuals with CAA and Alzheimer's disease. In addition, *APOE4* status may play a role in this association and additional studies could explore the mediating or moderating role of *APOE4* status on the association between Aβ and PVS.

Vascular dysfunction is strongly linked to the development of AD and it is hypothesized that vascular factors may play a key role in the pathogenesis of the disease (Sweeney et al., 2019). Our findings further support a link between breakdown of the cerebral vasculature and development of AD pathophysiological changes. Future studies are warranted to directly evaluate how PVS and the glymphatic system may be involved in the development of AD.

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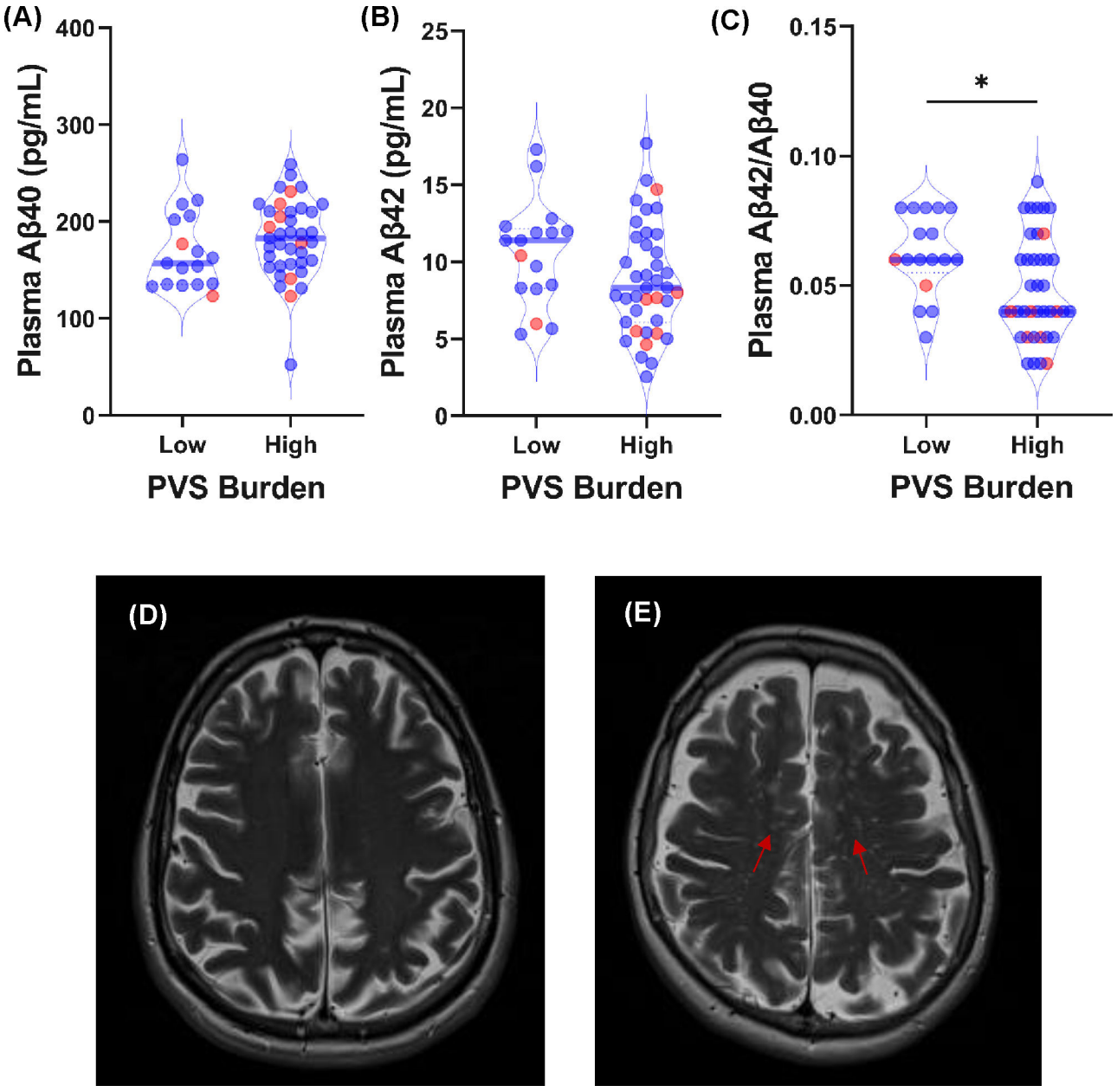


**Figure I. Plasma levels of (A) Aβ40 and (B) Aβ42 and (C)Aβ42/Aβ40 ratio by (D) Low and (E) High Enlarged Perivascular Spaces Burden**

*Note:* Red data points represent MCI participants.

**Table I.**

Participant Characteristics, Demographics and Vascular Risk Factors

| | All (N = 56) | High PVS Burden (N = 39) | Low PVS Burden (N = 17) | p-value |
|---|---|---|---|---|
| **Age (Years), M (SD)** | 68.2 (6.5) | 68.7 (6.7) | 66.8 (6.1) | .316 |
| **Sex (Male), N (%)** | 17 (30.4) | 9 (23.1) | 8 (47.1) | .073 |
| **Education (Years), M (SD)** | 16.2 (2.5) | 16.4 (2.3) | 15.8 (3.0) | .446 |
| **Aβ40 (pg/mL), M (SD)** | 178.4 (40.0) | 182.3 (40.0) | 169.4 (39.9) | .273 |
| **Aβ42 (pg/mL), M (SD)** | 9.4 (3.6) | 8.8 (3.6) | 10.5 (3.4) | .097 |
| **Aβ42/40, M (SD)** | .05 (.02) | .05 (.02) | .06 (.02) | .018 |
| ***APOE4* Carrier, N (%)[1]** | 30 (58.8) | 22 (61.1) | 8 (53.3) | .607 |
| **Vascular Risk Factors, N (%)[2]** | | | | |
| **Hypertension** | 19 (34.5) | 13 (33.3) | 6 (37.5) | .768 |
| **Dyslipidemia** | 23 (41.8) | 18 (46.2) | 5 (31.3) | .309 |
| **Diabetes** | 5 (9.1) | 2 (5.1) | 3 (18.8) | .110 |
| **Smoking History** | 20 (36.4) | 13 (33.3) | 7 (43.8) | .466 |
| **TIA** | 2 (3.6) | 2 (5.1) | 0 (0.0) | .356 |
| **Cardiovascular Disease** | 8 (14.5) | 8 (20.5) | 0 (0.0) | .050 |
| **Left Ventricular Hypertrophy** | 2 (3.6) | 2 (5.1) | 0 (0.0) | .356 |
| **Atrial Fibrillation** | 4 (7.3) | 4 (10.3) | 0 (0.0) | .183 |
| **White Matter Hyperintensities[3]** | 19 (34.5) | 16 (42.1) | 3 (17.6) | .078 |

*Note: P*-values reported are based on two-tailed t-tests and chi-square tests, not correcting for age.

[1] Missing for 2 participants with low PVS and 3 participants with high PVS burden.

[2] Missing for 1 participant with low PVS burden.

[3] White matter hyperintensities were scored using the Fazekas scale and frequency of scores over 1 is reported; missing for 1 participant with high PVS.