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Background

- **Enlarged perivascular spaces (PVS)** are fluid-filled structures surrounding small cerebral blood vessels that have been implicated in both vascular dementia/vascular cognitive impairment (VaD/VCI)¹ and Alzheimer's disease (AD).²
- Though historically viewed as independent causes of dementia, growing evidence suggests that mixed dementia is more common than previously recognized, most often involving co-occurring Alzheimer's and vascular pathology.³
- To elucidate the relative vascular and neurodegenerative contributions to PVS pathology, this study examined PVS volumes and their associations with established vascular and neurodegenerative imaging markers, across controls, individuals with AD, VaD/VCI, and mixed dementia.

Aims

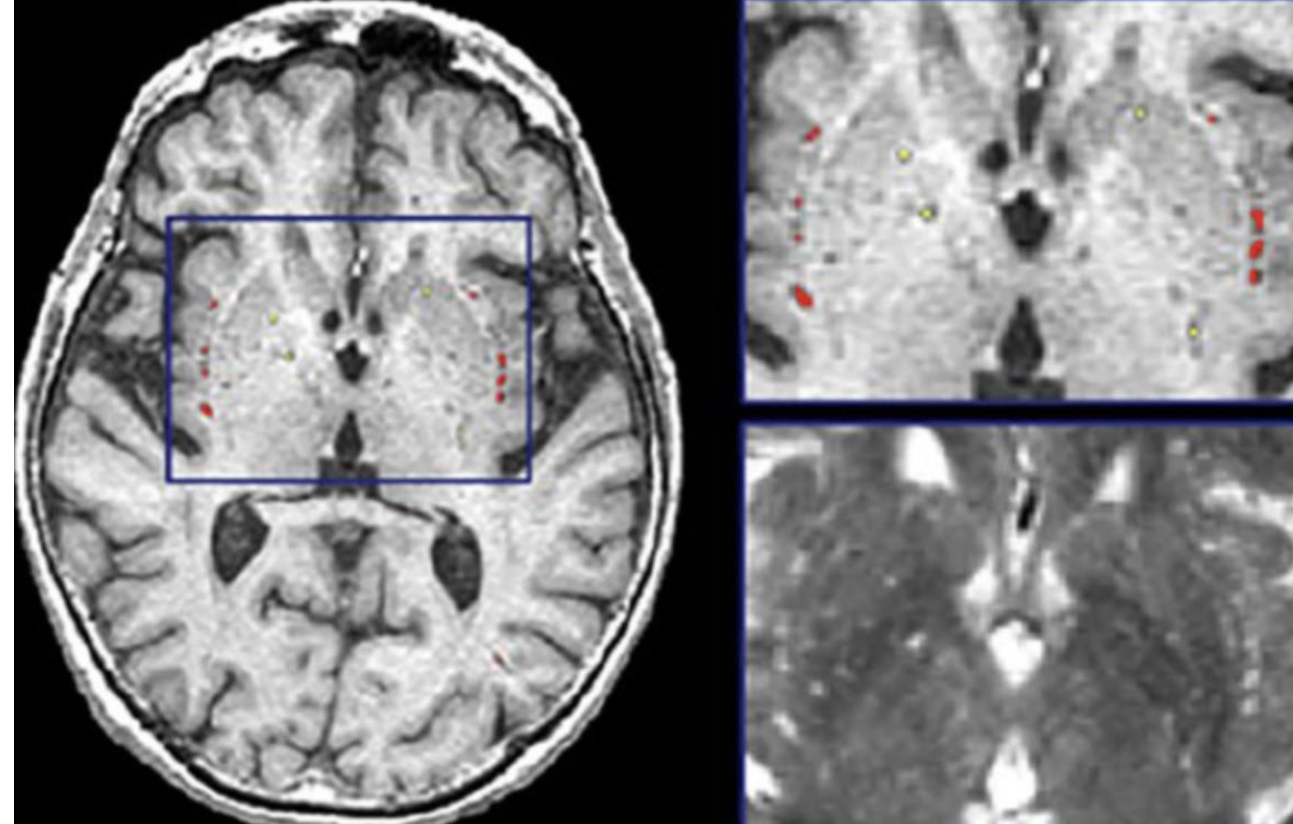
- Quantify and compare the extent of regional PVS volume in individuals with no dementia (ND), AD, VaD/VCI, or mixed AD+VaD/VCI
- Examine associations between PVS volume and other MRI markers of vascular injury and neurodegeneration

Methods

This cross-sectional study used data from the longstanding **Sunnybrook Dementia Study**

- Participants were classified into one of four groups based on reviewed physician diagnosis of AD,⁴ VaD/VCI (i.e. cerebrovascular disease; CVD),⁵ both AD+VaD/VCI, or no dementia (ND)
- 1.5 Tesla, T1-weighted MRI scans were quantified and processed using the Semi-Automatic Brain Region Extraction pipeline to obtain volumetrics for all neuroimaging markers
- Brain atrophy was assessed as brain parenchymal fraction (BPF), defined as the ratio of normal-appearing white and gray matter (NAWM + NAGM) to TIV
- Hippocampal volume were derived using a fully automated template-library-based segmentation approach

Statistical Analyses:

- Analysis of covariance (ANCOVA) was used to determine differences in basal ganglia (BG) and white matter (WM) PVS volume and post-hoc comparisons performed on estimated marginal means with Bonferroni correction for multiple comparisons
 - Three sets of linear regression models incorporating interaction terms were used to assess PVS associations:
 - i. Whole-group model including AD, CVD, and $AD \times CVD$ terms
 - ii. Two-way interaction model including both $PVS \times AD$ and $PVS \times CVD$ terms
 - iii. Three-way interaction model including a $PVS \times AD \times CVD$ term
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- Figure 1.** Example of PVS (red + yellow) segmentation

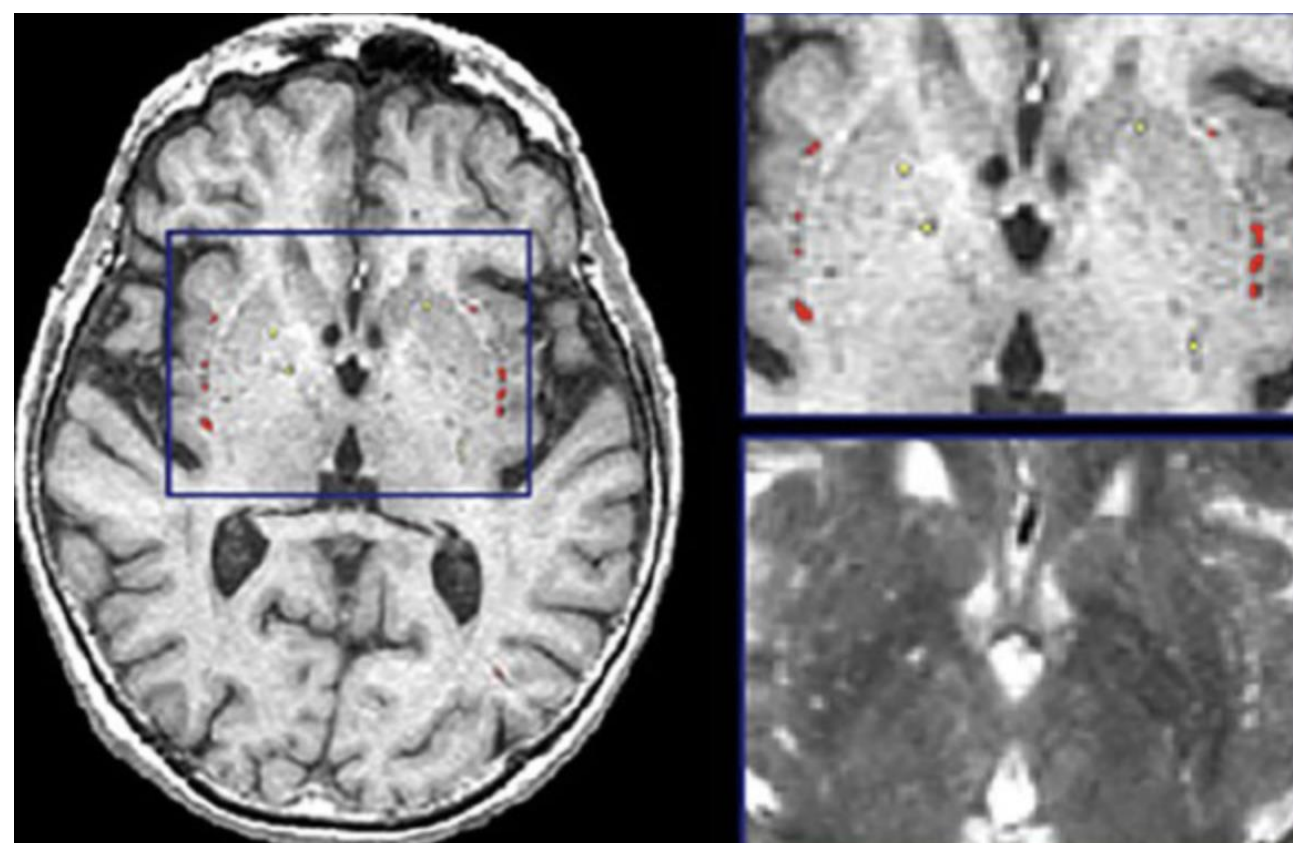


Figure 1. Example of PVS (red + yellow) segmentation

- All base analyses were adjusted for age, sex, and TIV
- Sensitivity analyses were further adjusted for vascular risk factors (hypertension, hyperlipidemia, diabetes) and imaging markers (WMH, lacunes, stroke volume), as well as AD risk factors (APOE- $\epsilon 4$ status), due to incomplete availability of variables

Results

Table 1. Participant characteristics

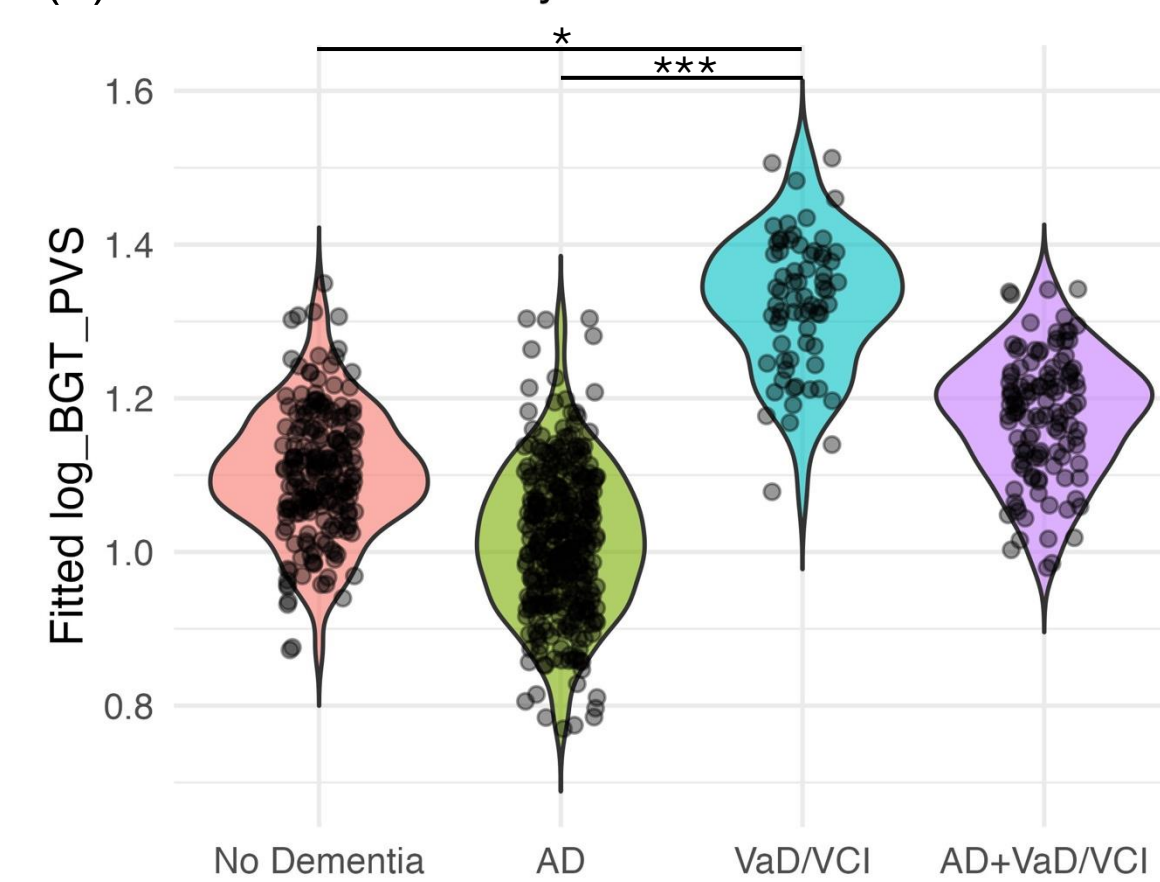
Characteristic	ND (n=201)	AD (n=328)	VaD/VCI (n=70)	AD+VaD/VCI (n=118)	p-value ^a
Age	68 (9)	71 (10)	71 (9)	76 (6)	<.001
Sex (female)	125 (62%)	158 (48%)	27 (39%)	69 (58%)	<.001
Years of Education	15 (3)	14 (4)	14 (4)	14 (3)	<.001
MMSE Total	28 (2)	23 (5)	26 (3)	23 (4)	<.001
Hypertension ^b	36 (22%)	103 (33%)	39 (62%)	59 (53%)	<.001
Hyperlipidemia ^b	40 (29%)	92 (30%)	31 (50%)	34 (31%)	0.016
Diabetes ^b	10 (6.2%)	15 (4.8%)	8 (13%)	7 (6.3%)	0.2
APOE-ε4 carriers ^b	27 (39%)	150 (57%)	16 (35%)	49 (54%)	0.005
Total Intracranial Volume (cm ³)	1204.54 (121.35)	1216.92 (140.95)	1211.0 (130.99)	1207.32 (144.57)	0.8

Continuous variables are reported as mean (SD), and categorical variables are reported as N (%).

^aKruskal-Wallis rank sum test for continuous variables; Pearson's Chi-squared or Fisher's exact test for categorical variables.

^bAll summaries are based on available data for each variable, see Figure 4 caption.

(a) BG PVS Volume by Cohort



(b) WM PVS Volume by Cohort

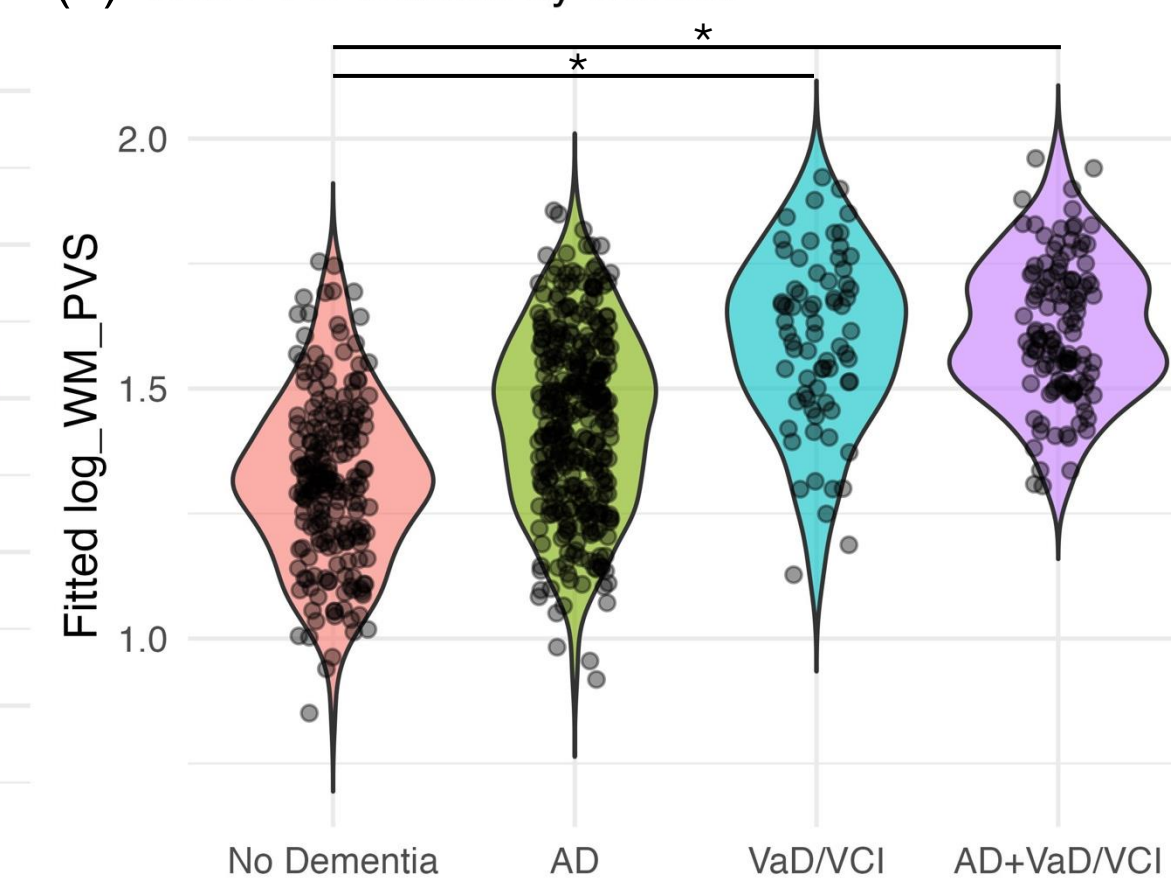
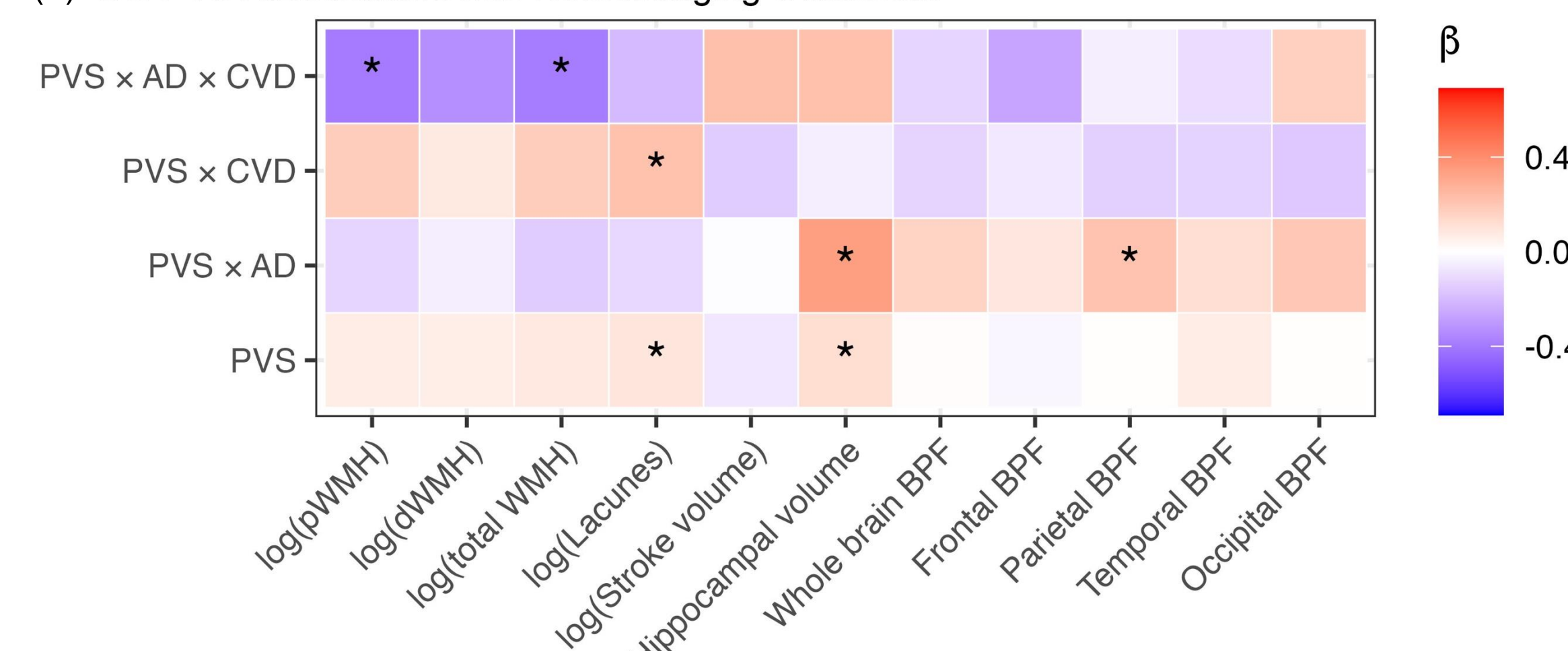


Figure 2. ANCOVA results examining differences in (a) BG and (b) WM PVS volumes between groups after adjusting for base covariates. Pairwise comparisons were Bonferroni corrected.

* $p < .05$, *** $p < .0001$

- VaD/VCI groups demonstrated the highest WM and BG PVS volume
- The AD group demonstrated the lowest BG PVS burden

(a) BG PVS Associations with Neuroimaging Outcomes



(b) WM PVS Associations with Neuroimaging Outcomes

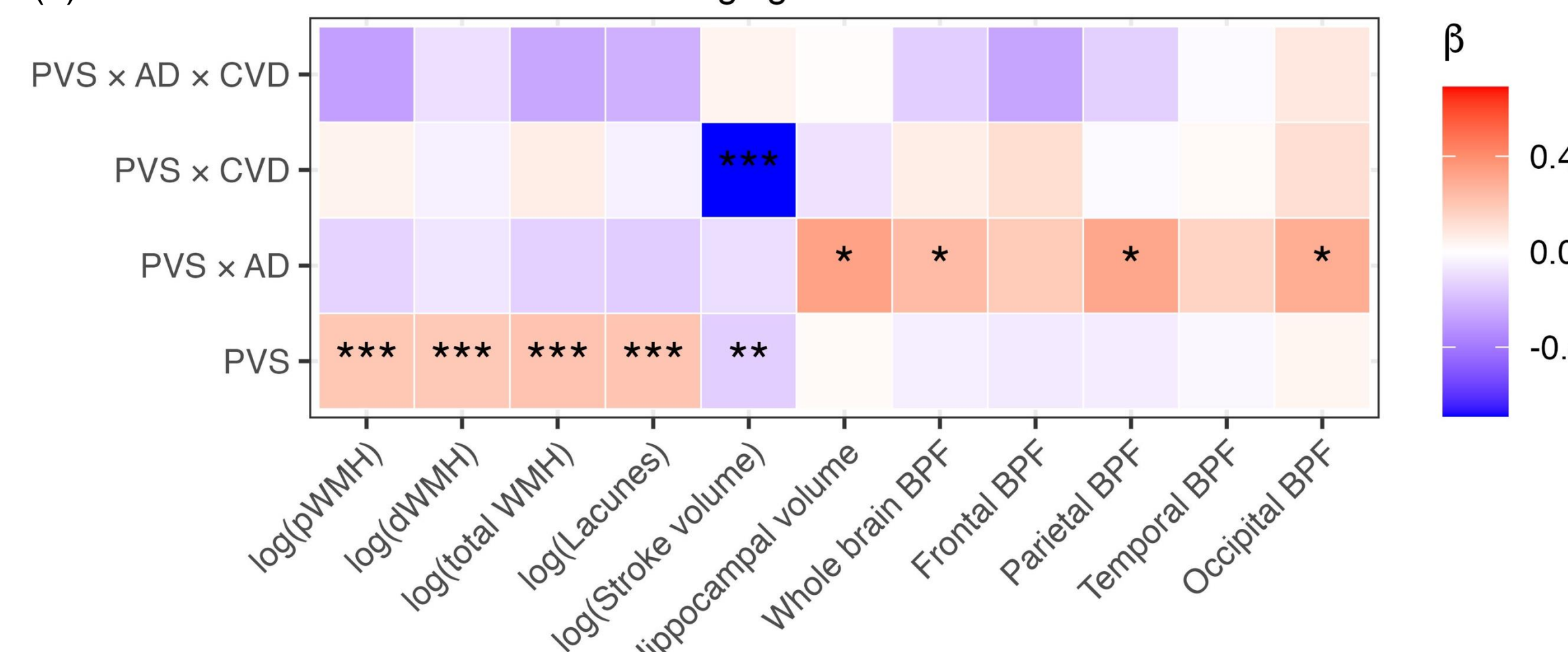


Figure 3. Heatmaps displaying (a) BG and (b) WM PVS associations with vascular and neurodegenerative markers after FDR correction. PVS = main effect across whole sample; PVS $\times$ AD = effect modification of PVS-outcome association by AD status; PVS $\times$ CVD = effect modification of PVS-outcome association by CVD status; PVS $\times$ AD $\times$ CVD = effect modification of PVS-outcome association beyond sum of individual disease effects. * $p^{FDR} < .05$, ** $p^{FDR} < .001$, *** $p^{FDR} < .0001$

Results

- PVS interacted with AD status to predict lower brain atrophy and higher hippocampal volume
- PVS interacted with CVD status to predict higher lacunes and lower stroke volume
- PVS interacted with both AD and CVD status to predict lower white matter hyperintensities (WMH)

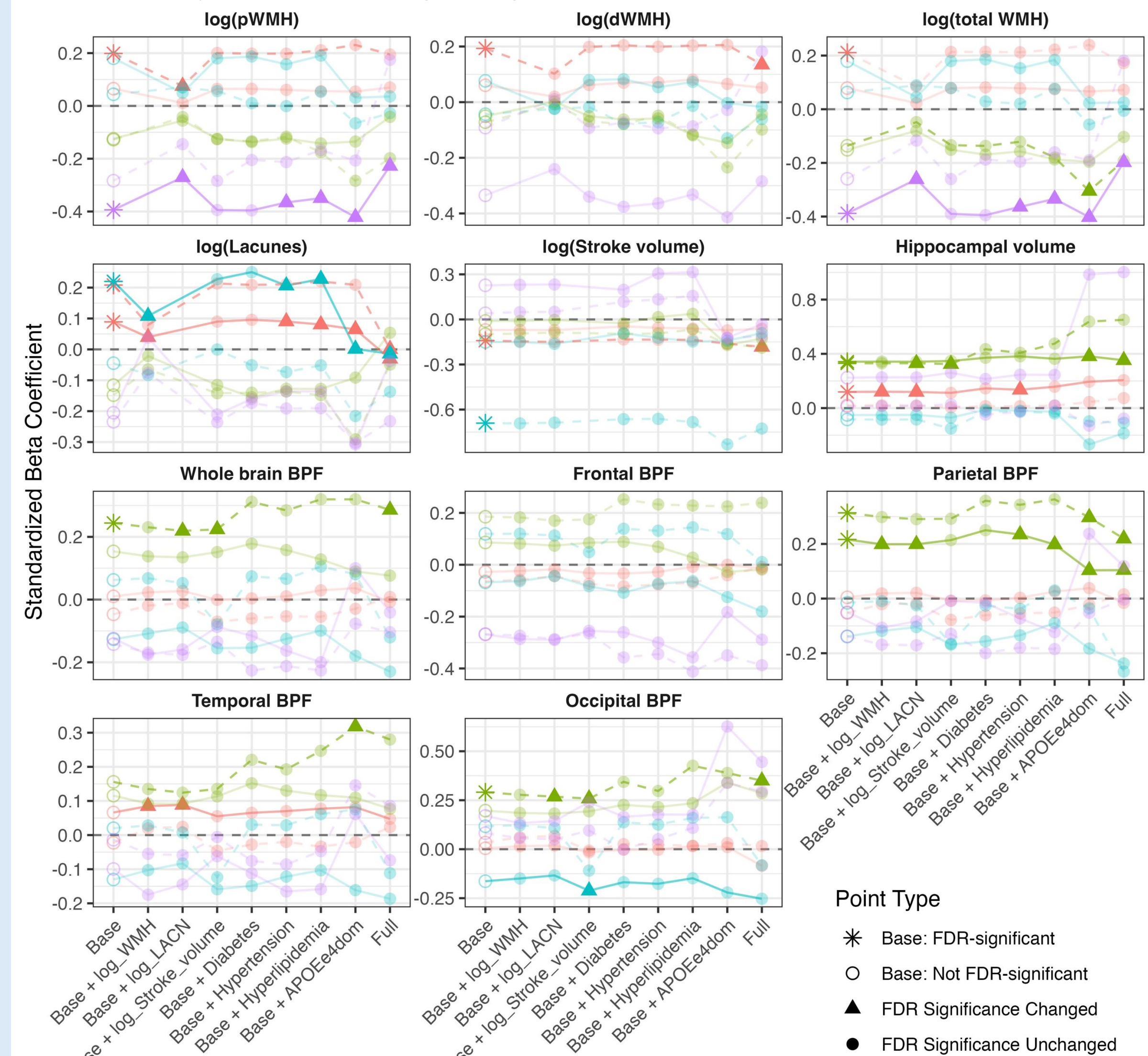


Figure 4. Sensitivity models displaying standardized beta coefficients for models after further adjustment for additional covariates. Point type indicates base and model significance after FDR-correction. Total number of subjects with available hypertension, hyperlipidemia, diabetes, APOE-ε4 genotype, and hippocampal volume were 648, 613, 647, 471, and 374 respectively, out of 717 participants.

Conclusions

- ❖ PVS volumes varied across groups and displayed region- and disease-specific associations with vascular and neurodegenerative markers.
- ❖ Results suggest differing underlying mechanisms for PVS enlargement across AD and CVD, and may reflect distinct involvement of small-vessel and glymphatic function across dementia subtypes.

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Acknowledgements