

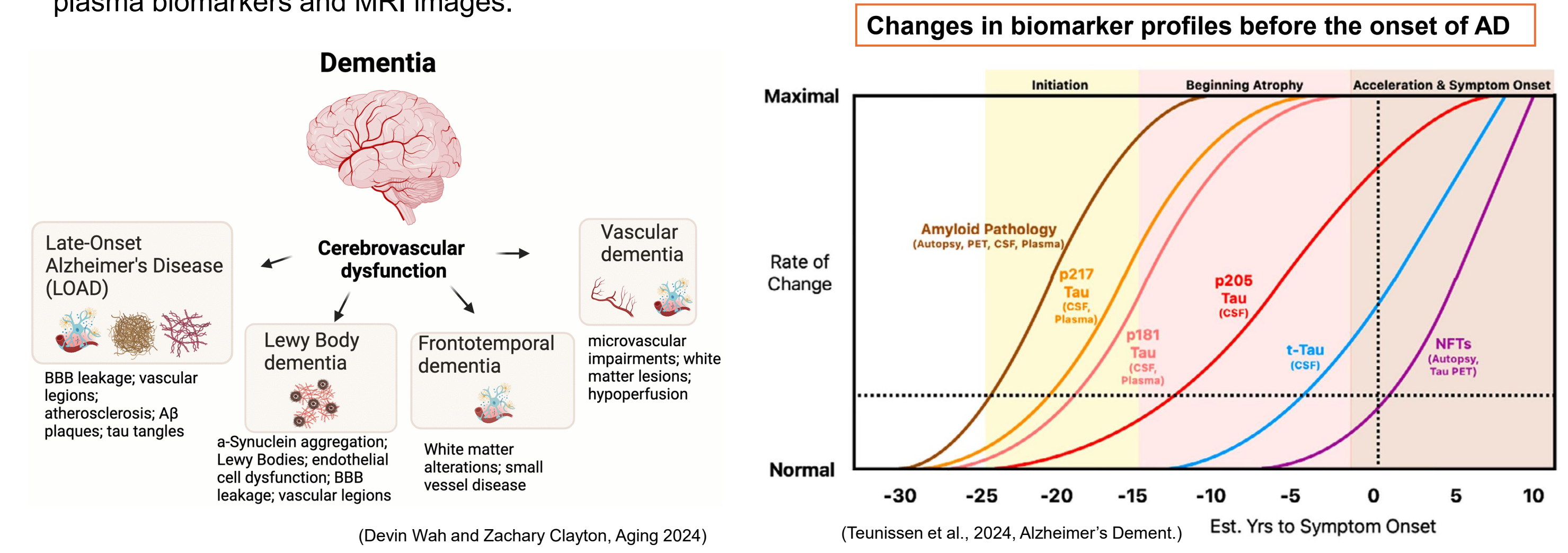
Sex-Specific Patterns of Microvascular Pathology and Hippocampal Atrophy in Alzheimer's Disease: Evidence from a Community-Based MRI and Blood Biomarkers

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INTRODUCTION

- Plasma biomarkers for Alzheimer's disease (AD) are indicators of neuropathological changes.
- However, plasma biomarkers may not consistently indicate the presence or absence of a pathology.
- Discrepant biomarker levels are observed in some cognitively normal subjects and clinically diagnosed AD patients.
- Some asymptomatic individuals showed significant change in biomarker levels of AD and some symptomatic individuals showed no evidence of biomarker levels.
- The purpose of this study is to understand the discordant biomarker levels among clinically diagnosed CN and AD using plasma biomarkers and MRI images.



MATERIALS & METHODS

- We measured plasma phosphorylated tau 181 (P-tau181), phosphorylated tau 217 (P-tau217), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) in 685 participants from the Washington Heights-Inwood Columbia Aging Project (WHICAP; 29.61% non-Hispanic White, 30.62% African American, and 37.30% Caribbean Hispanic).
- Participants were classified as biomarker-positive based on a plasma P-tau217 cutoff of 0.39 pg/mL. 295 were biomarker-negative cognitively normal controls (BM-CTL), 183 were biomarker-positive preclinical individuals (BM+Preclin), 21 were biomarker-negative individuals with dementia (BM-Dem), and 33 were biomarker-positive individuals with Alzheimer's disease (BM+AD).
- We compared white matter hyperintensity (WMH) volume, hippocampal volume, the number of silent brain infarcts (SBI), microbleeds, GFAP, and NfL across the four biomarker-defined groups (BM-CTL, BM+Preclin, BM-Dem, and BM+AD). We also performed analogous analyses using P-tau181-defined groups to assess the consistency of the findings with those obtained using P-tau217-based classification.
- Associations were evaluated using analysis of covariance (ANCOVA), adjusting for age, sex, and ethnicity. For MRI phenotypes, field strength and intracranial volume were included as additional covariates.

Table 1: Study participants by P-tau217 defined clinical groups

	Biomarker negative control (BM-CTL)	Biomarker positive Preclinical (BM+ Preclinical)	Biomarker negative dementia (BM-Dem)	Biomarker positive Alzheimer's disease (BM+AD)
N	295 (50.8%)	183 (38.9%)	21 (4.4%)	33 (5.8%)
Age, Mean(SD)	74.98 (6.15)	78.25 (6.82)	81.33 (8.42)	82.42 (7.14)
Women (%)	69%	60.01%	66.67%	69.70%
Education, Mean (SD)	12.15 (4.82)	12.74 (4.92)	7.05 (4.22)	8.87 (5.30)
APOE ε4 (%)	68 (23.05%)	58 (31.69%)	5 (23.81%)	13 (39.39%)
Microbleeds, N (Positive %)	224 (12.94%)	118 (18.64%)	15 (13.33%)	21 (9.52%)
Silent brain infarcts, N (Positive %)	294 (0.30)	182 (0.38)	19 (0.47)	30 (0.43)
White matter hyperintensity volume (cm ³), Mean (SD)	10.81 (13.92)	11.26 (12.90)	18.91 (18.6)	25.23 (24.125)
Hippocampus volume (mm ³), Mean (SD)	6977.13 (770.865)	6902.635 (929.185)	6244.795 (603.06)	6736.88 (713.32)

RESULTS

Figure 1. Comparison analysis of plasma biomarker and MRI phenotypes among P-tau217 defined groups

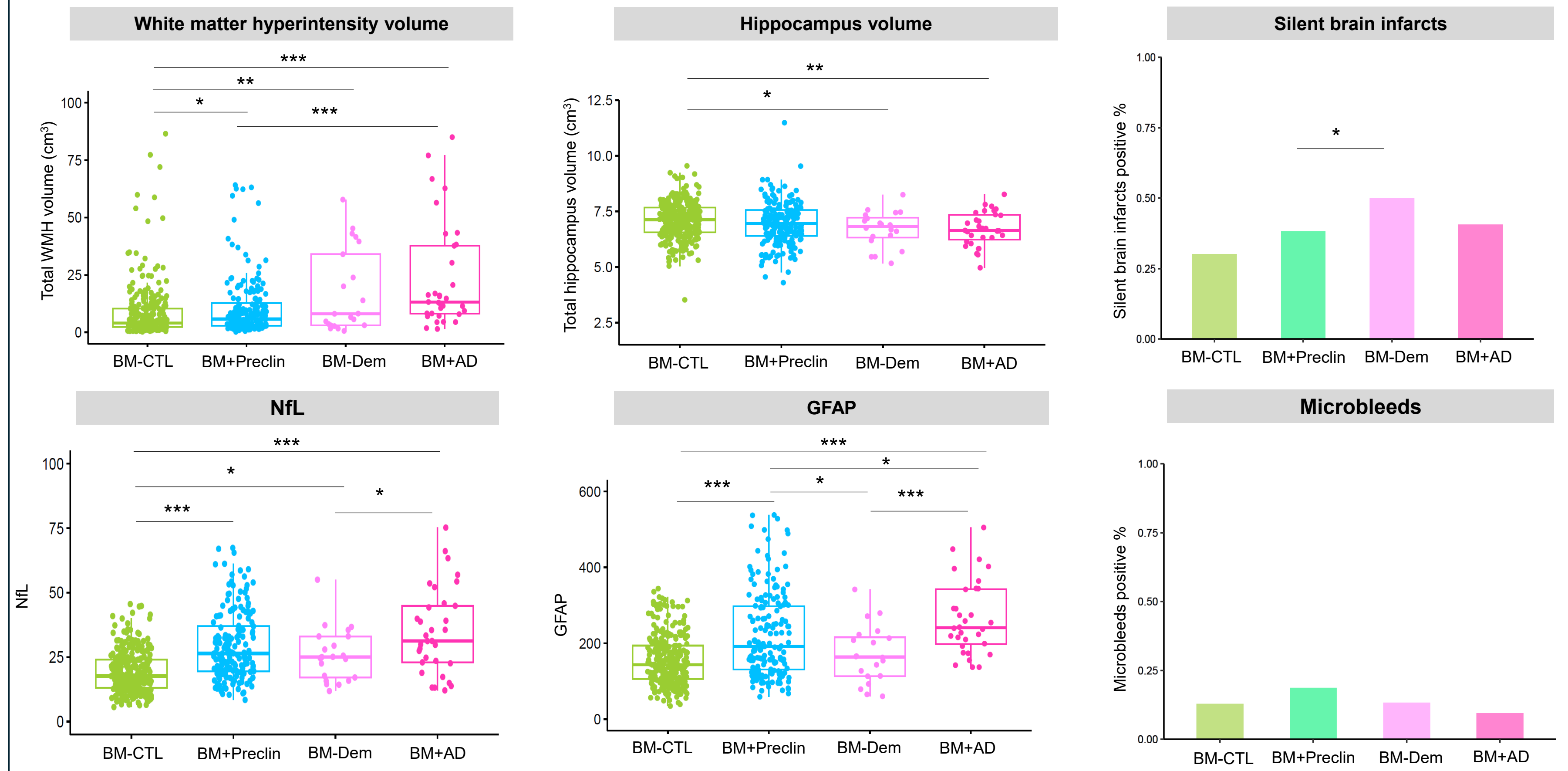
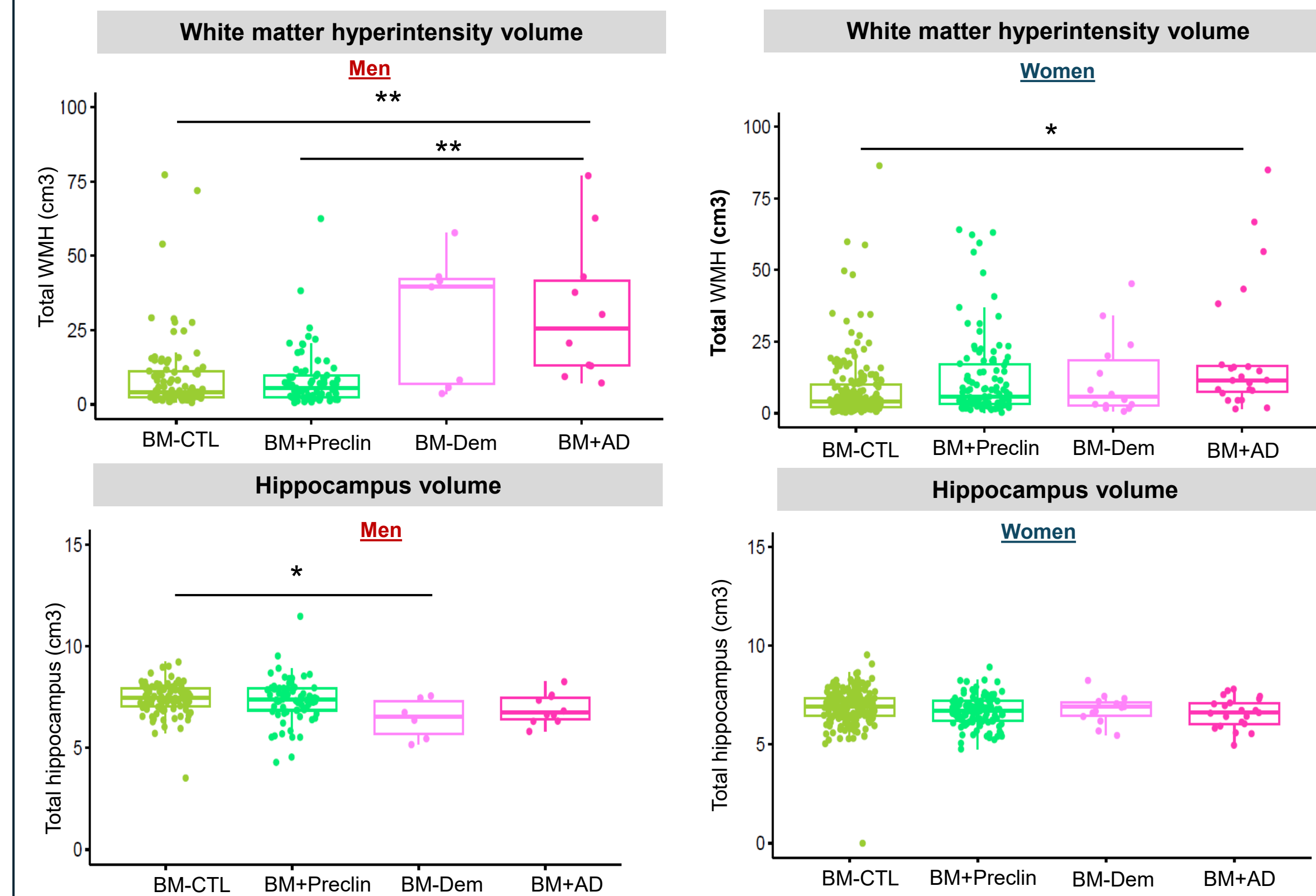


Figure 2. Sex stratified analyses on MRI measures



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CONCLUSION

- Biomarker-positive individuals with AD and other dementias exhibited greater WMH burden, more silent brain infarcts, and smaller hippocampal volumes, highlighting the contribution of cerebral small vessel disease to dementia and AD.
- Compared with BM-CTL, BM+Preclin individuals, BM-Dem, and BM+AD had increased NfL and GFAP levels, consistent with increased neurodegeneration and neuroinflammation.
- Within P-tau217-defined groups, men showed a higher cerebrovascular burden compared to women.
- The results indicate that cerebrovascular disease is consistently involved in dementia either directly or as a coincident pathology in AD. Specifically, men appearing to be at highest risk.
- These results underscore the need to incorporate both blood-based biomarkers and structural imaging in the evaluation of patients with dementia.

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