Sex-Specific Associations of White Matter Hyperintensity and Alzheimer's Disease Blood-based Biomarkers in Midlife: The CARDIA Study

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Background

- White matter hyperintensity (WMH) is a well-established cerebral small vessel disease marker that is strongly age-dependent and contributes to cognitive decline even in young and middle-aged adults.
- Prior studies have reported controversial relationships with WMH and amyloid-β (Aβ) and tau burden among older adults across Alzheimer's disease (AD) spectrum, and whether these associations differ by sex remains unclear.
- Whether WMH is associated with Aβ and tau burden in midlife, a critical window for early AD prevention, remains unknown.

Aims

- To investigate the cross-sectional associations between WMH and AD blood-based biomarkers, and whether sex modifies these relationships in midlife adults.

Methods

- We included participants (age range: 53-68 years) who completed both brain magnetic resonance imaging (MRI) and AD plasma biomarkers assessments from the Coronary Artery Risk Development in Young Adults (CARDIA) study.
- Total and lobar WMH volume were measured by 3-Tesla brain MRI, log transformed and normalized for intracranial volume using the residual approach.
- The main outcomes were plasma Aβ42/40, p-tau217, and p-tau217/Aβ42, which were measured in an Fujirebio Lumipulse G1200 automated immunoassay system.
- Using multivariable regression models, we first examined the main effects between WMH and AD plasma biomarkers; then tested interactions by sex and performed sex-stratified analyses, adjusting for demographics, APOE ε4 status, renal function, and diabetes.

Results: Participants characteristics stratified by sex

- Compared with women, men were more likely to have diabetes, had greater WMH volume in occipital and parietal regions, lower plasma Aβ42/40 ratio, and higher plasma p-Tau 217/Aβ42 ratio (all p<0.05).
- Sex modified the associations of total, temporal, and parietal WMH with AD blood-based biomarkers (p for evidence of interaction<0.1).
- Total and regional WMH volumes were associated with AD plasma biomarkers in men, but not women.

Baseline Characteristics Mean (SD) or N (%)	Overall N = 543	Men N = 239	Women N = 304	*p* value
Age, years	61.7 (3.4)	61.6 (3.5)	61.7 (3.4)	0.74
Race				0.13
White	333 (61)	155 (65)	178 (59)	
Black	210 (39)	84 (35)	126 (41)	
Education, years	15.2 (2.7)	15.2 (2.8)	15.2 (2.6)	0.94
APOE ε4 carries	171 (31)	70 (29)	101 (33)	0.33
Diabetes	54 (9.9)	38 (16)	16 (5.3)	<0.001
Log_{10}(total WMH +1), mL	3.04 (0.54)	3.08 (0.52)	3.01 (0.55)	0.13
AD blood-based biomarkers, pg/mL (log_{10}-transformed)				
Aβ42/40	-1.03 (0.05)	-1.03 (0.05)	-1.02 (0.05)	0.03
p-Tau 217	-1.08 (0.21)	-1.07 (0.21)	-1.08 (0.22)	0.30
p-Tau 217/ Aβ42	-2.51 (0.22)	-2.49 (0.20)	-2.52 (0.23)	0.003

Results: Sex-specific associations between WMH and AD plasma biomarkers

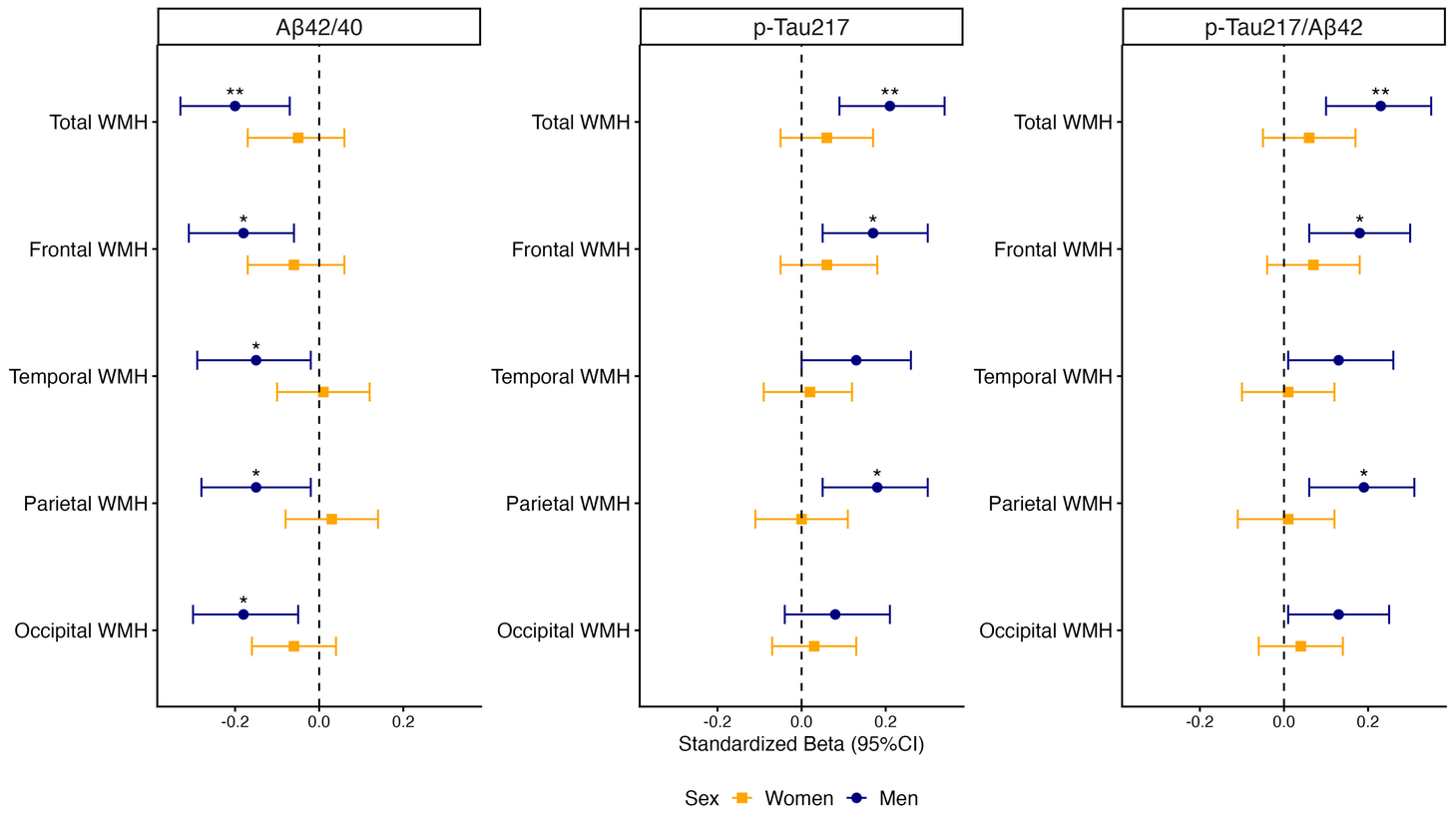


Figure. Comparison of sex-specific associations between WMH and AD plasma biomarkers
Values represent standardized β with 95% confidence interval after adjusting for age, race, education, estimated glomerular filtration rate, APOE4 status, and diabetes.
* FDR-adjusted p<0.05, ** FDR-adjusted p<0.01.

Take home message

- Sex modified the associations of WMH volume and AD plasma biomarkers among midlife adults, whereby these relationships were observed in men only.
- Future longitudinal studies are warranted to validate these sex-specific findings and elucidate underlying mechanisms.

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