

The Modulating Role of Sex in the Relationship Between Blood Cholesterol Markers and Neurovascular Pathology



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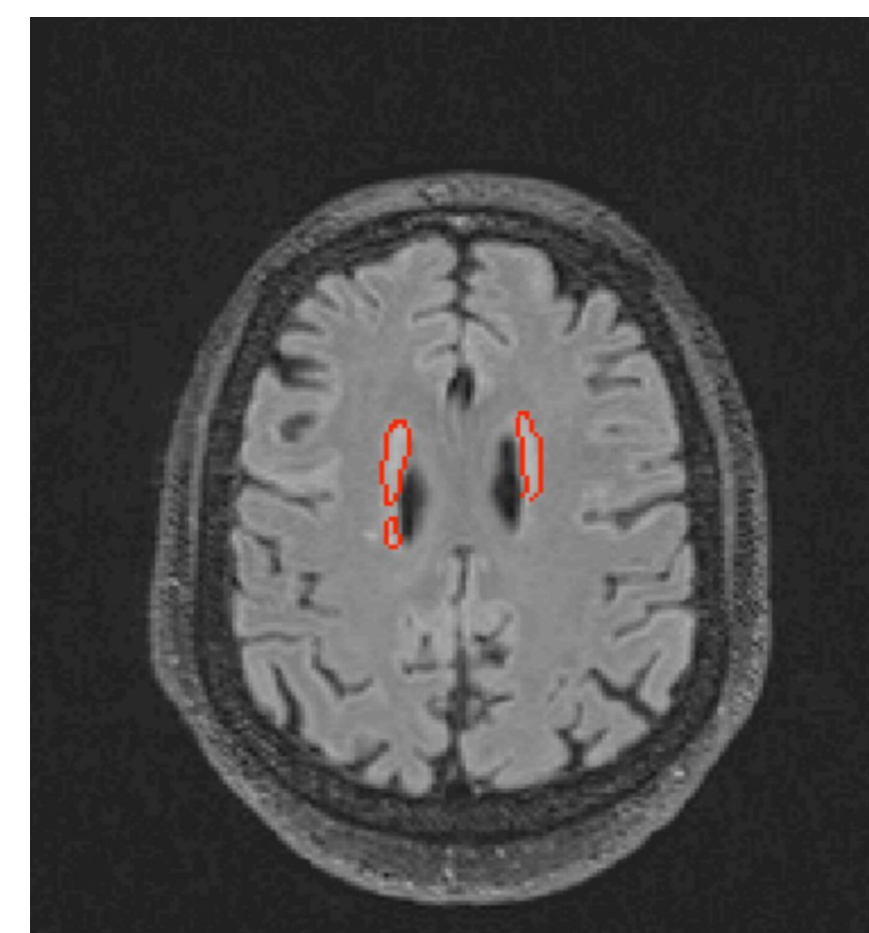
INTRODUCTION

- White Matter Hyperintensities (WMHs) reflect vascular injury and are associated with Alzheimer's disease-related neurodegeneration and metabolic dysfunction^{1,2,3}.

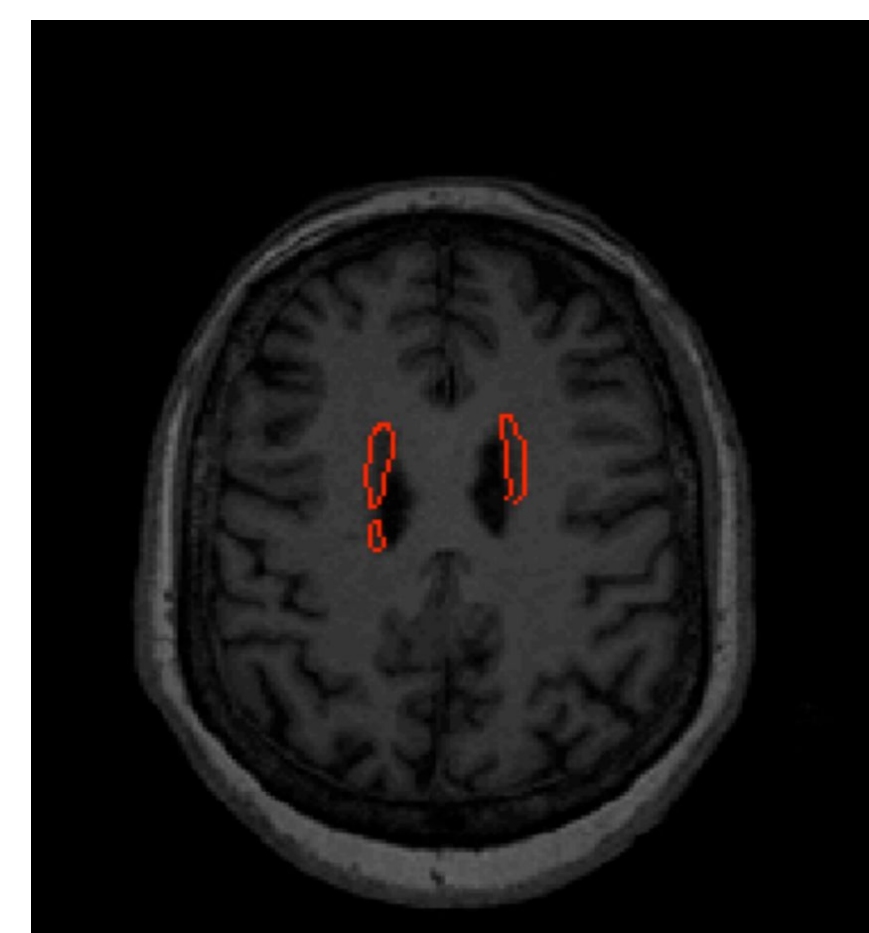
⇒ Pathologically arisen from blood brain barrier dysfunction and disruptions related to cerebral small-vessel disease⁴.

- A higher ratio of high-density lipoprotein cholesterol (HDL-c) to low-density lipoprotein cholesterol (LDL-c) has been associated with less severe WMHs⁵.
- Males and females have distinct vascular phenotypes and hormonal profiles that may contribute to sex-specific WMH risk.
- Circulating lipid levels and WMH burden vary by sex, but whether sex modulates associations between cholesterol and WMH burden remains unclear.

OBJECTIVE: Examine whether sex modifies the relationship between circulating cholesterol and WMH volume in a multi-ethnoracial cohort of cognitively unimpaired older adults.



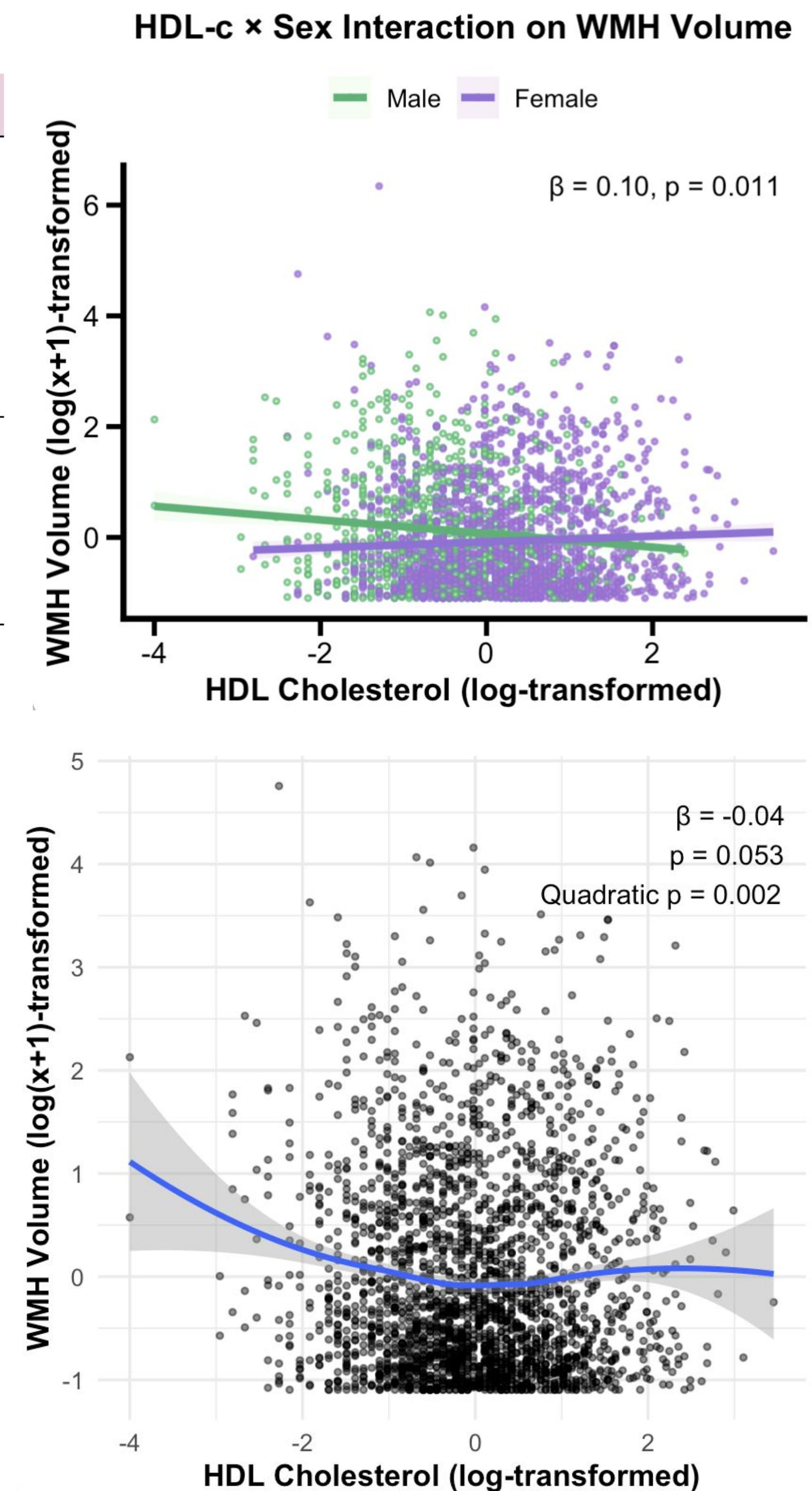
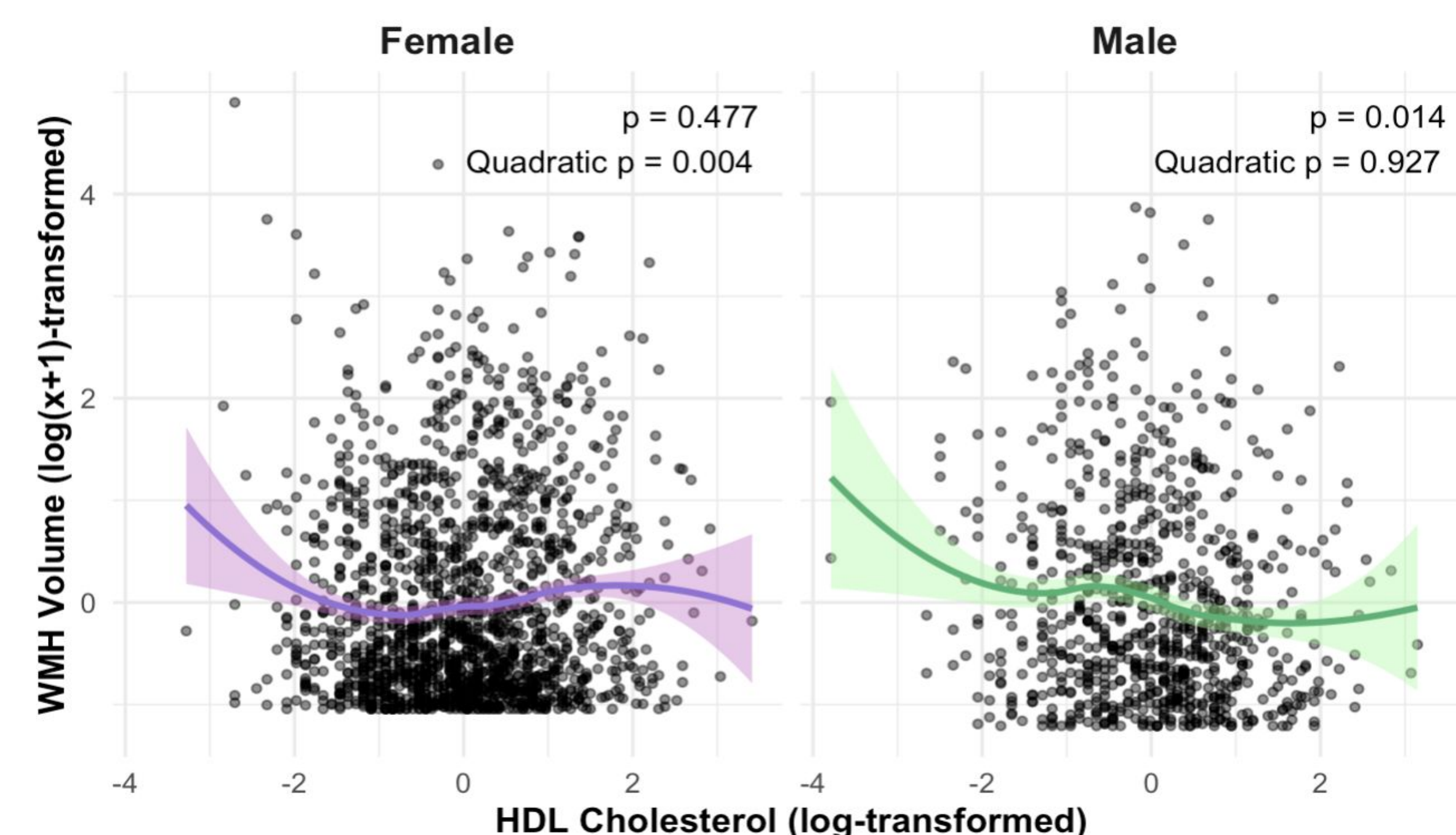
FLAIR + Seg Outline



MPRAGE + Seg Outline

Table 1. Cohort Demographics

	Male	Female
N	843	1648
Ethnicity (n)	373 NHW / 295 H / 175 AA	621 NHW / 620 H / 407 AA
APOE-ε4 (+/-)	227+ / 616-	468+ / 1180-
Mean age (years)	65.8 ± 8.2	64.6 ± 8.5
Mean education (years)	14.1 ± 4.4	13.5 ± 4.1
Diabetes (n, %)	206 (24.4%)	359 (21.8%)
Dyslipidemia (n, %)	594 (70.5%)	1120 (68.0%)
Hypertension (n, %)	578 (68.6%)	1002 (60.8%)
Mean BMI	30.2 ± 5.5	30.7 ± 7.0
Mean WMH volume (mm ³)	3.3 ± 6.5	2.9 ± 12.4
Mean HDL-c (mg/dL)	48.7 ± 12.5	60.4 ± 16.0
Mean LDL-c (mg/dL)	97.5 ± 32.9	107.0 ± 33.5
Mean Triglyceride (mg/dL)	123.2 ± 65.5	118.1 ± 56.7



METHODS

Study cohort: 2,491 cognitively unimpaired (CU) participants from the Health and Aging Brain Studies - Health Disparities (HABS-HD) dataset.

WMH quantification: SPM's lesion growth algorithm (applied to T2 FLAIR Magnetic Resonance Images)

Statistical modeling: Initial associations between HDL-c, LDL-c, & triglycerides with WMH were examined using both linear and second-degree polynomial terms ($scale(x) + I(scale(x)^2)$) to test for non-linearity. Interaction terms with sex were included in base lm models.

- Covariates:** age, sex, years of education, APOE-ε4 positivity, ICV, MRI scanner, BMI, diabetes, hypertension, smoking history.
- We applied false discovery rate (FDR) method multiple comparison corrections.

RESULTS

There was a significant HDL-c×sex interaction on WMH volume ($\beta = 0.1$; FDRp = 0.034)

⇒ **Higher HDL-c associated with lower WMH in males** ($\beta = -0.08$; p = 0.013) **but not females** ($\beta = -0.02$; p > 0.1)

There was a trend-level association between higher triglycerides with greater WMH volume ($\beta = 0.04$; FDRp = 0.065) **and between higher HDL-c with lower WMH volume** ($\beta = -0.04$, FDRp = 0.077)

HDL-c was the only cholesterol marker non-linearly associated with WMH ($\beta = 0.04$; FDRp = 0.006)

CONCLUSIONS

- Sex moderated the relationship between HDL-c and WMH such that greater HDL-c levels were associated with lower WMH in males only
- Circulating cholesterol differentially associate with WMH, and HDL-c uniquely demonstrates a non-linear relationship with WMH burden

These findings support further investigating sex-based factors influencing circulating cholesterol levels in relation to WMH with age, and motivate sex-specific prevention strategies targeting lipid dysregulation in populations at-risk for AD.

ACKNOWLEDGMENTS

Thank you to the HABS-HD study team, participants, and the Braskie Laboratory at USC. This work was supported by the National Institutes of Health for the Health And Aging Brain Study - Health Disparities (U19A078109).

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