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Introduction

Whether life-course lipid burden shapes midlife brain health, and whether that differs by sex, is unclear.

- Sustained dyslipidemia promotes endothelial dysfunction, harming cerebral perfusion and small-vessel integrity [1,2]
- Dyslipidemia's atherosclerotic effects reach the cerebral microvasculature, contributing to white matter hyperintensities (WMH) [3,4]
- Prior lipid-brain findings are inconsistent [5] and may be sex-specific [6], potentially reflecting the menopause transition [7]
- This study tests whether a novel cumulative dyslipidemia metric (cAUC) predicts midlife WMH, and whether this differs by sex

Bogalusa Heart Study Sample

Lipid burden was tracked from childhood through midlife brain imaging.

- Community-based cohort followed from childhood into midlife since 1972
- Included: ≥2 lipid exams (1985–2010) + brain MRI (2017–2025)
- Key terms:**
- WMH – T2/FLAIR MRI marker of cerebral small-vessel disease (aging, vascular risk, cognitive decline)
- cAUC – area-under-the-curve summary of cumulative HDL, LDL, and triglyceride deviation from optimal levels

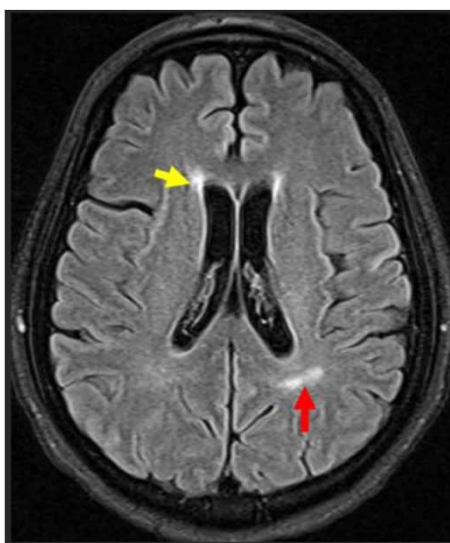


Figure 1. Examples of white matter hyperintensities on brain MRI. Source: Penn State Health Medical Update (2022), white matter hyperintensities MRI.

Quantifying Life-Course Dyslipidemia Burden

cAUC captures cumulative lipid burden across adulthood, not just a single snapshot.

- % deviation from optimal HDL, LDL, triglycerides calculated at each exam (1985–2010) using AHA/ACC thresholds
- Cumulative exposure = area under the deviation-age curve ÷ years observed (AUC rate)
- Composite Dyslipidemia Burden (cAUC) = sum of the 3 AUC rates, z-scored within sex

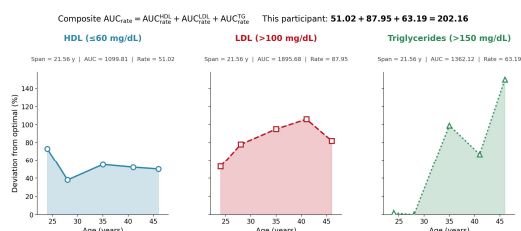


Figure 2. Example composite dyslipidemia burden (cAUC) calculation for a representative participant.

WMH and gray matter volume came from validated structural MRI.

- 3T scanner (GE Discovery, 32-ch head coil), T1-weighted BRAVO + axial FLAIR; WMH and GMV/TIV quantified via established methods

Statistical Analysis

Sex-stratified regression tested whether the cAUC–WMH link depends on sex.

- WMH_INT (rank-based inverse normal transformed); GMV/TIV analyzed untransformed
- Sex-stratified OLS with HC3 standard errors; adjusted for age at MRI and race
- Sensitivity analyses added statin duration and hypertension; pooled model tested sex × cAUC interaction

Sample Characteristics

The sample (N = 215) was mostly female and White American.

- N = 215; 65% female; 81% White American; mean age 56.8 ± 5.3y at MRI
- Men carried significantly greater cAUC than women (0.61 vs. 0.44, p = 0.006) (Table 1)

Characteristic	Overall (n=215)	Female (n=139)	Male (n=76)	P value
Demographics				
Age at MRI, y	56.8 ± 5.3	56.4 ± 5.1	57.5 ± 5.5	0.172
Female, %	64.7	100.0	0.0	N/A
White American, %	80.5	74.1	92.1	N/A
Black American, %	19.5	25.9	7.9	N/A
Dyslipidemia Burden (AUC rates)				
Composite dyslipidemia burden	0.50 ± 0.41	0.44 ± 0.39	0.61 ± 0.43	0.006**
HDL	0.16 ± 0.12	0.16 ± 0.12	0.17 ± 0.13	0.701
LDL	0.26 ± 0.23	0.21 ± 0.23	0.34 ± 0.23	<0.001***
Triglycerides	0.08 ± 0.25	0.07 ± 0.27	0.10 ± 0.21	0.423
Brain MRI Outcomes				
WMH volume, mL, median (IQR)	0.17 (0.04–0.42)	0.16 (0.04–0.37)	0.25 (0.05–0.43)	0.356
WMHINT, mean ± SD	0.00 ± 0.99	−0.04 ± 0.96	0.09 ± 1.04	0.375
Lipid-Lowering Therapy				
Ever statin use, %	10.7	8.6	14.5	0.274
Statin duration, y	4.12 ± 3.67	4.14 ± 3.70	4.11 ± 3.82	0.988
Comorbidities				
Hypertension, %	26.0	26.6	25.0	0.924
Diabetes, %	6.0	7.2	3.9	0.512
BMI, kg/m ²	29.2 ± 6.8	29.2 ± 7.4	29.3 ± 5.8	0.840
Current smoking, %	20.5	20.0	21.7	0.983

Values are mean ± SD unless otherwise indicated. *P < 0.05, **P < 0.01, ***P < 0.001. N/A = Not Applicable. Significance: *p < 0.05, **p < 0.01, ***p < 0.001.

Results

The cAUC–WMH association was sex-specific.

- Women (n=139): each 1-SD increase in cAUC linked to 0.13-SD higher WMH_INT ($\beta = 0.129$, 95% CI [0.014, 0.245], $p = 0.029$)
- Men (n=76): association not significant, opposite direction ($\beta = -0.155$, 95% CI [−0.371, 0.061], $p = 0.161$), despite men carrying greater cAUC (Figure 3)
- Formal sex × cAUC interaction confirmed, adjusting for statin exposure ($\beta = 0.239$, 95% CI [0.006, 0.472], $p = 0.045$)
- cAUC was not linked to gray matter volume in either sex; no single lipid fraction independently predicted WMH – supporting cAUC as a cumulative measure

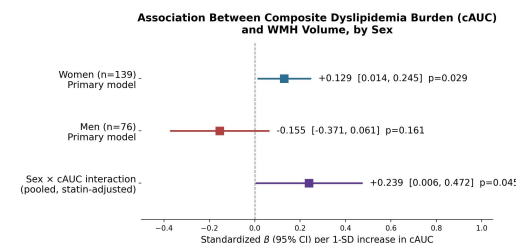


Figure 3. Association between composite dyslipidemia burden (cAUC) and WMH volume, by sex.

Conclusion

Life-course lipid burden is linked to brain injury in women – supporting early, sex-aware lipid monitoring.

- Greater life-course dyslipidemia burden was linked to higher midlife WMH volume in women, but not men
- Confirmed by formal sex × cAUC interaction testing
- Supports a life-course neurovascular framework linking lipid dysregulation to later cerebrovascular injury
- Reinforces the 2026 ACC/AHA Guideline's call for vigilant lipid monitoring from early adulthood, particularly in women

References, Contact Info, and Funding

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