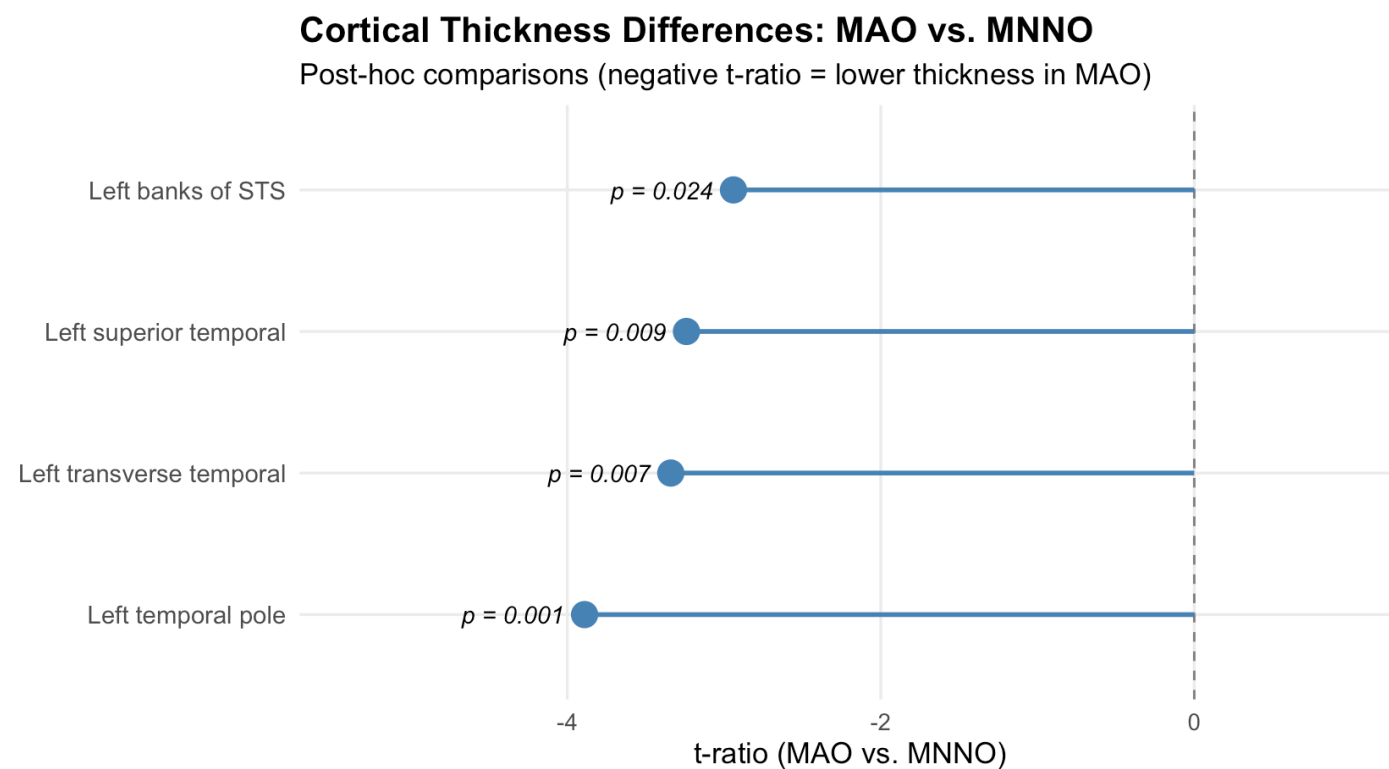


Effect of Midlife Obesity and Insulin Resistance on Brain Cortical Thickness: Insights into Alzheimer’s Disease Risk

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Targeting obesity and metabolic dysfunction (e.g. lifestyle modification interventions combining weight management) in midlife may offer a critical window to mitigate or delay the progression of Alzheimer's disease before the onset of overt clinical symptoms.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES															
Recent evidence from large-scale neuroimaging cohorts and meta-analyses confirms that midlife obesity and insulin resistance independently elevate risk of Alzheimer’s disease (AD). However, their synergistic effects on neurodegenerative trajectories remain underexplored. Using multimodal imaging, this study investigates whether co-occurring obesity (BMI ≥ 30 kg/m²) and insulin resistance are correlated to cortical thickness and volume in AD-related regions of brain on MRI, alongside whole-brain and regional amyloid-β and tau burden on PET scan.	A cohort of one hundred and eleven intact midlife adults (mean age 50.04±6.23 years, 31.5% male, 54% obese) completed 3T structural MRI, [11C] PiB amyloid PET, AV-1451 tau PET imaging, and metabolic profiling. Insulin resistance was operationalized as HOMA-IR ≥ 1.9. Cortical parcellation and subcortical segmentation were performed with FreeSurfer v7.1.1, incorporating rigorous quality assurance and targeted manual corrections. Standardized uptake value ratios (SUVRs) for amyloid and tau were computed relative to cerebellar cortex; global amyloid burden was expressed in Centiloid units derived from PiB data. Participants were stratified into four groups according to obesity and insulin resistance status: metabolically normal non-obese (MNNO), metabolically abnormal non-obese (MANO), metabolically normal obese (MNO), and metabolically abnormal obese (MAO). Between-group differences in AD-related brain regions were evaluated using one-way ANCOVA, covarying for age and sex, followed by FDR-adjusted pairwise comparison.	Between group cortical thickness metrics differed significantly in left transverse temporal thickness (P-value= 0.013), left temporal pole thickness (P-value= 0.015), left superior temporal thickness (P-value= 0.016), left banks of the superior temporal sulcus thickness (P-value= 0.034), and right precuneus thickness (P-value= 0.035). Post-hoc comparison showed that left temporal pole thickness(t-ratio= -3.89; P-value= 0.001), left transverse temporal thickness (t-ratio= -3.34; P-value= 0.007), left superior temporal thickness(t-ratio= -3.24; P-value= 0.009), and left banks of the superior temporal sulcus thickness (t-ratio= -2.94; P-value= 0.024) were significantly lower in MAO compared with MNNO. We did not observe a between group difference in volume metrics, amyloid burden, tau burden, or whole brain amyloid Centiloid. Cortical Thickness Differences: MAO vs. MNNO Post-hoc comparisons (negative t-ratio = lower thickness in MAO) <table><tr><th>Region</th><th>t-ratio (MAO vs. MNNO)</th><th>p-value</th></tr><tr><td>Left banks of STS</td><td>-2.94</td><td>0.024</td></tr><tr><td>Left superior temporal</td><td>-3.24</td><td>0.009</td></tr><tr><td>Left transverse temporal</td><td>-3.34</td><td>0.007</td></tr><tr><td>Left temporal pole</td><td>-3.89</td><td>0.001</td></tr></table>	Region	t-ratio (MAO vs. MNNO)	p-value	Left banks of STS	-2.94	0.024	Left superior temporal	-3.24	0.009	Left transverse temporal	-3.34	0.007	Left temporal pole	-3.89	0.001	Our findings suggest that midlife obesity is associated with thinner left banks of the superior temporal sulcus, right precuneus, left temporal poles, left transverse temporal, and left superior temporal. These changes suggest that obesity and metabolic status may mediate early AD risk, with the absence of tau differences consistent with a subclinical disease stage.	Alford S, Patel D, Perakakis N, Mantzoros CS. Obesity as a risk factor for Alzheimer's disease: weighing the evidence. <i>Obes Rev.</i> 2018; 19(2): 269-280. Fitzpatrick AL, Kuller LH, Lopez OL, et al. Midlife and late-life obesity and the risk of dementia: cardiovascular health study. <i>Arch Neurol.</i> 2009; 66(3): 336-342. CONTACT Mona Mirbeyk, MD Visiting Researcher Washington University in St Louis mmona@wustl.edu ALZHEIMER'S ASSOCIATION AAIC 26
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