

Associations Between Systemic Inflammatory Markers and Structural and Molecular Brain Changes in Cognitively Normal Middle-Aged Adults

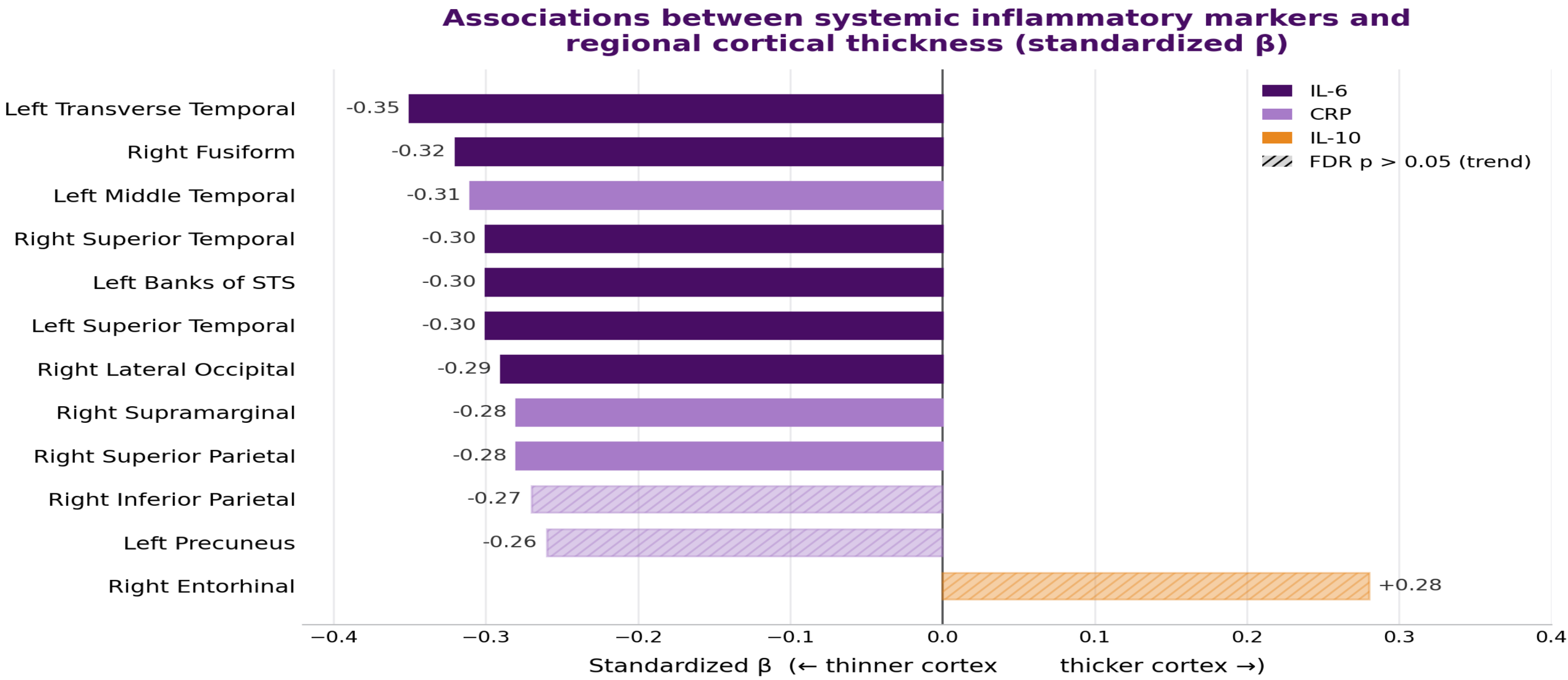
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In cognitively normal midlife adults, higher systemic inflammation was associated with reduced cortical thickness in AD-vulnerable temporal and parietal regions, suggesting inflammation marks early structural vulnerability before clinical symptoms emerge.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Background: Systemic inflammation has been implicated in Alzheimer’s disease (AD) pathogenesis and cognitive decline, with prior work linking individual inflammatory markers to neurodegenerative processes. Pro- and anti-inflammatory cytokines and acute-phase proteins may differentially relate to early brain changes that precede symptoms, but their links to brain structure and AD pathology in cognitively normal adults remain poorly characterized. Objective: To examine associations between systemic inflammatory markers (IL-6, IL-10, TNF-α, CRP) and multimodal neuroimaging markers of AD vulnerability, cortical thickness and volume, plus amyloid PET, in cognitively normal adults.	Sample: 142 cognitively normal adults (49.9 ± 6.1 years; 62% female) underwent 3T structural MRI and peripheral inflammatory marker assessment; a subset also completed amyloid and tau PET imaging. Inflammatory markers: IL-6, IL-10, TNF-α, and CRP were log-transformed to address non-normality. Structural MRI: Cortical thickness and regional volumes within Late-Onset AD (LOAD) regions were derived using FreeSurfer 7.1.1 with standard quality control. PET: Amyloid PET data were processed with the PET Unified Pipeline; standardized uptake value ratios (SUVR) used the cerebellar cortex as reference. Analysis: Multiple linear regression adjusted for age, sex, and education, with heteroscedasticity-consistent robust standard errors and false discovery rate (FDR) correction for multiple comparisons.	Higher systemic inflammation was associated with reduced cortical thickness across multiple AD-vulnerable temporal, parietal, and occipital regions after FDR correction (Table 2). IL-6 → reduced cortical thickness left transverse temporal ($\beta = -0.35$), right and left superior temporal, left banks of the STS, right fusiform, and right lateral occipital ($\beta = -0.29$ to -0.35). CRP → reduced cortical thickness left middle temporal ($\beta = -0.31$), right supramarginal, right superior and inferior parietal, and left precuneus ($\beta = -0.26$ to -0.28). IL-10 → higher right entorhinal cortical thickness ($\beta = +0.28$). Associations were strongest (FDR $p < 0.05$) in temporal and superior parietal regions. See Table 2 for full statistics.	Higher systemic inflammatory markers were linked to reduced cortical thickness in AD-vulnerable regions, indicating early structural change in cognitively normal midlife adults. IL-6 and CRP showed the most consistent inverse associations with cortical thickness, concentrated in temporal and parietal regions, suggesting inflammation may preferentially affect cortical microarchitecture. IL-10 showed a distinct positive association with entorhinal thickness, pointing to marker-specific relationships that warrant further study. Together, these findings implicate systemic inflammation in early structural vulnerability and underscore the need to study inflammation-related mechanisms as potential intervention targets in preclinical disease stages.	1. Xie J, Van Hoecke L, Vandenbroucke RE. The impact of systemic inflammation on Alzheimer’s disease pathology. <i>Front Immunol.</i> 2022;12:796867. doi:10.3389/fimmu.2021.796867 2. Marsland AL, Gianaros PJ, Kuan DCH, Sheu LK, Krajina K, Manuck SB. Brain morphology links systemic inflammation to cognitive function in midlife adults. <i>Brain Behav Immun.</i> 2015;48:195–204. doi:10.1016/j.bbi.2015.03.015 3. Satizabal CL, Zhu YC, Mazoyer B, Dufouil C, Tzourio C. Circulating IL-6 and CRP are associated with MRI findings in the elderly: the 3C-Dijon Study. <i>Neurology.</i> 2012;78(10):720–727. doi:10.1212/WNL.0b013e318248e50f CONTACT  Mobina Amanollahi Mallinckrodt Institute of Radiology Washington University in St. Louis [Mobina@wustl.edu] ALZHEIMER’S ASSOCIATION AAIC>26

Associations between inflammatory markers and cortical thickness in AD-vulnerable regions (significant findings)

ROI	Marker	β (std)	SE (HC3)	p	p-FDR	R ²	Adj. R ²
Left Transverse Temporal	IL-6	−0.35	0.0138	0.00028	0.006	0.312	0.283
Right Superior Temporal	IL-6	−0.30	0.0098	0.00055	0.006	0.223	0.190
Left Banks of STS	IL-6	−0.30	0.0113	0.00628	0.047	0.103	0.064
Left Middle Temporal	CRP	−0.31	0.0156	0.00815	0.047	0.121	0.084
Right Supramarginal	CRP	−0.28	0.0091	0.01345	0.050	0.121	0.083
Right Fusiform	IL-6	−0.32	0.0115	0.01426	0.050	0.077	0.038
Right Lateral Occipital	IL-6	−0.29	0.0122	0.01734	0.050	0.077	0.037
Left Superior Temporal	IL-6	−0.30	0.0111	0.01867	0.050	0.183	0.148
Right Superior Parietal	CRP	−0.28	0.0093	0.01951	0.050	0.112	0.074
Right Inferior Parietal	CRP	−0.27	0.0080	0.02229	0.051	0.147	0.110
Left Precuneus	CRP	−0.26	0.0085	0.03007	0.063	0.145	0.108
Right Entorhinal	IL-10	0.28	0.0312	0.03505	0.067	0.066	0.026



Negative β = reduced cortical thickness. Solid bars survive FDR correction ($p \leq 0.05$); hatched bars are trend-level. Models adjusted for age, sex, education.