

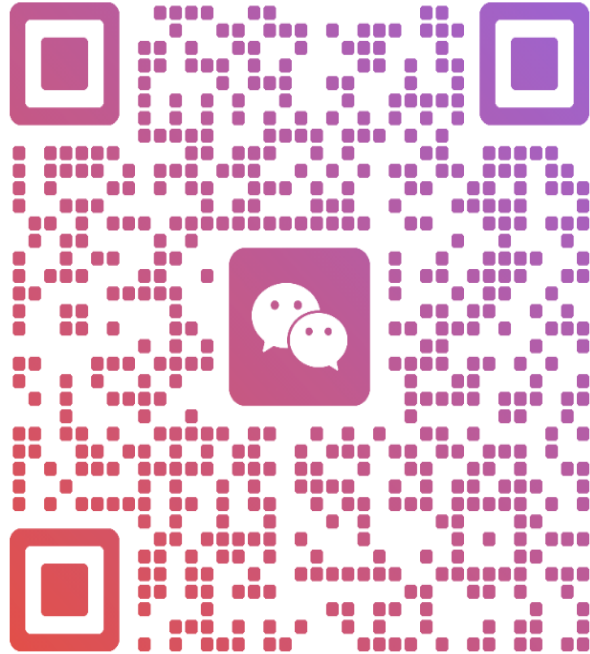
Systemic Inflammation As A Causal Driver Of Alzheimer's Disease: Evidence From Mendelian Randomization Of Circulating Cytokines

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Using Mendelian randomization to evaluate the causal effects of circulating inflammatory cytokines on in Alzheimer’s disease (AD) risk, we found that increased interleukin-6 signaling was associated with a higher risk of AD. These findings support targeting systemic inflammation may represent a promising avenue for AD prevention and therapeutic strategies.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Chronic systemic inflammation has been implicated in Alzheimer’s disease (AD) pathogenesis; however, whether inflammatory biomarkers play a causal role remains uncertain. We used Mendelian randomization (MR) to evaluate the causal effects of circulating inflammatory cytokines on AD risk.	Genetic instruments for circulating levels of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and other cytokines were obtained from large GWAS meta-analyses. Summary-level AD data were ourced from IGAP. Two-sample MR analyses were performed using IVW as the primary method, supplemented by sensitivity analyses to assess pleiotropy and heterogeneity.	IVW MR analysis demonstrated that genetically predicted increased interleukin-6 (IL-6) signaling was associated with a higher risk of Alzheimer’s disease (OR per 1-SD increase = 1.21, 95% CI: 1.08-1.36, P = 0.002). In contrast, genetically predicted circulating C-reactive protein (CRP) levels showed no significant association with AD risk (OR = 1.02, 95% CI: 0.93-1.12, P = 0.67). Tumor necrosis factor-α (TNF-α) demonstrated a modest but non-significant trend toward increased AD risk (OR = 1.09, 95% CI: 0.98-1.22, P = 0.11). Sensitivity analyses using weighted median and MR-Egger approaches yielded directionally consistent results. There was little evidence of horizontal pleiotropy based on MR-Egger intercept tests (P > 0.20) and Cochran’s Q statistics indicated low heterogeneity.	This MR study provides genetic evidence supporting a causal role of specific inflammatory pathways, particularly IL-6 signaling, in AD development. Targeting systemic inflammation may represent a promising avenue for AD prevention and therapeutic strategies.	Zhao, J.H., et al., Genetics of circulating inflammatory proteins identifies drivers of immune-mediated disease risk and therapeutic targets. Nat Immunol. 2023; 24:1540-1551. CONTACT  Peng Tang, MD Department of Geriatric Neurology Shaanxi Provincial People's Hospital No. 256, Youyi West Road Xi'an 710068, China Tel. +86 2985251331 tango@spph-sx.ac.cn 