

Immune, blood-brain barrier, and metabolic biomarkers mediate gut-brain axis crosstalk in Alzheimer’s disease

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INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Gut microbiota may influence Alzheimer's disease (AD) pathogenesis by modulating host homeostasis. However, population-based causal evidence linking gut dysbiosis to Alzheimer’s disease pathogenesis, especially via immune, vascular, and metabolic pathways, remains insufficient.	We performed Mendelian randomization (MR) and colocalization analysis on 629 gut microbiota features and 2,103 immune, blood-brain barrier (BBB), and metabolic biomarkers regarding the risk of AD and cerebrospinal fluid (CSF) pathological biomarkers. Fig.1 Schematic overview of the study design. GWAS summary data included taxonomy and pathway profiles for gut microbiota, as well as blood metabolites, immune markers, blood-brain barrier(BBB)-related biomarkers, and Alzheimer's disease (AD) phenotypes, including cerebrospinal fluid (CSF) pathological biomarkers. In the univariable framework, bidirectional two-sample mendelian randomization (MR) was conducted to explore causal relationships, followed by enrichment analysis for biological process annotation. In the multivariable framework, mendelian randomization-Bayesian Model Averaging (MR-BMA) was applied to identify key gut microbiota associated with AD risk. Mediation analysis assessed the intermediary role of circulating biomarkers in the gut microbiota-AD interaction, while colocalization analysis validated the MR findings.	We identified that mucin-degraders, short-chain fatty acid (SCFA) producers, and Programmed Cell Death Protein 1/Programmed Death-Ligand 1 (PD-1/PD-L1)-related biomarkers were associated with lower AD risk, while cardiovascular microbes, Amyloid-beta (Aβ)-related proteins, and lipoproteins were linked to higher risk. Increased AD risk was associated with decreased SCFA producers, branched-chain amino acids (BCAAs), and lactate, but with increased liver-disease microbes, fatty acids, and glycoprotein acetyls. Notably, <i>Desulfovibrionaceae</i> and <i>Methanobrevibacter</i> emerged as critical contributors to AD. <i>Erysipelotrichaceae</i> abundance inversely modulates CSF phosphorylated tau (p-tau) pathology while being increased by Aβ42 pathology, suggesting a microbiota-mediated feedback circuit in AD. Mediation analysis highlighted the role of CD28-CD8+ T cells, CD19 on IgD+ CD24+ B cells, glycoproteins, and low-density lipoprotein (LDL) in microbiota-gut-brain axis bidirectional communication. Colocalization analyses confirmed causal links between AD and LDL metabolism through shared variant rs7412 (posterior probability, PP=1.0), while revealing colocalized architecture for amyloid-tau copathology at rs71352238 (PP=1.0).	Our study reveals a bidirectional gut–brain feedback loop in AD, in which gut microbiota promote neuroinflammation and immune aging, while AD exacerbates gut dysbiosis via lipid metabolic dysregulation. This self-reinforcing mechanism involving immune signaling, BBB disruption, and SCFA imbalance offers potential targets for integrated microbiota-based interventions in AD prevention.	Li J, Yuan Z, Li J, et al. Immune, blood-brain barrier, and metabolic biomarkers mediate gut-brain axis crosstalk in alzheimer’s disease. <i>Biomarker Research</i>, 2025, 13(1): 137. CONTACT Presenting Author: Jincheng Li, Fudan University, Shanghai, China. Email: jinchengli23@m.fudan.edu.cn ALZHEIMER’S ASSOCIATION AAIC>26