

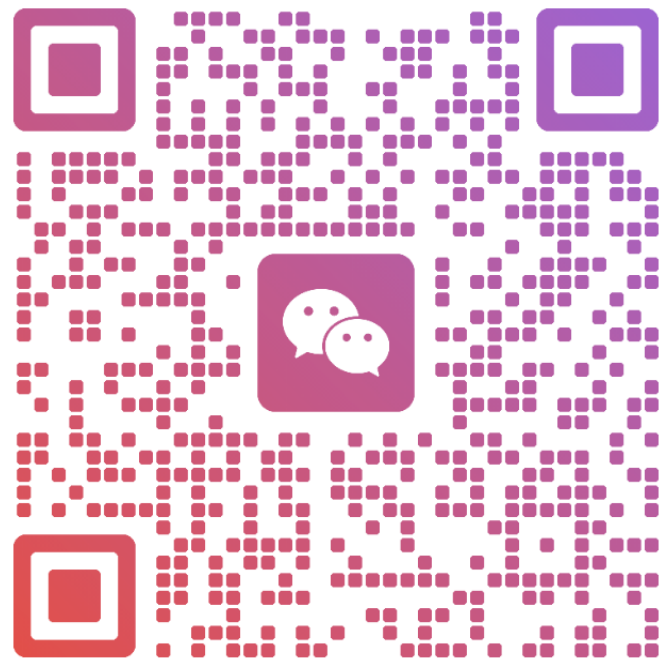
Gut Microbiota-derived Metabolites And Alzheimer's Disease: A Mendelian Randomization Analysis

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Using Mendelian randomization, we found that higher circulating trimethylamine N-oxide (TMAO) levels were associated with an increased risk of Alzheimer’s disease (AD) and short-chain fatty acid (SCFA)-related metabolites were associated with a substantially lower risk of AD. These findings highlight the gut-brain axis as a potential target for early AD prevention through dietary or microbiome-based interventions.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Emerging evidence suggests that gut microbiota may influence brain health through microbiota-derived metabolites, but causal evidence linking these metabolites to Alzheimer’s disease (AD) is lacking. We employed Mendelian randomization (MR) to investigate whether genetically predicted levels of gut microbiota-related metabolites causally affect AD risk.	Genetic instruments for microbiota-related metabolites, including short-chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO), were obtained from published metabolomics GWAS. AD summary statistics were sourced from IGAP. Two-sample MR analyses were conducted using IVW and complementary sensitivity methods to ensure robustness.	Genetically predicted higher circulating trimethylamine N-oxide (TMAO) levels were associated with an increased risk of Alzheimer’s disease (OR per 1-SD increase = 1.25, 95% CI: 1.10-1.42, P < 0.001). Conversely, genetically predicted short-chain fatty acid (SCFA)-related metabolites were inversely associated with AD risk (OR = 0.82, 95% CI: 0.71-0.95, P = 0.008). These associations remained robust across sensitivity analyses, including weighted median and MR-Egger methods. No evidence of significant horizontal pleiotropy was detected (MR-Egger intercept P > 0.15), and MR-PRESSO analyses did not identify influential outliers.	Our findings provide novel genetic evidence supporting a causal role of gut microbiota-derived metabolites in AD risk. These results highlight the gut-brain axis as a potential target for early AD prevention through dietary or microbiome-based interventions.	1. Wishart DS, et al., HMDB 4.0: the human metabolome database for 2018. Nucleic Acids Res. 2018;46:D608–D617. 2. Shin SY, et al., Multiple Tissue Human Expression Resource (MuTHER) Consortium. An atlas of genetic influences on human blood metabolites. Nat Genet. 2014;46:543–550.
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