

ORIGINAL RESEARCH ARTICLE

Causal association between constipation and white matter microstructure: A Mendelian randomization study

Cong Zhou^{1,2†}, Hailong Shen^{1†}, Shanling Ji¹, Shengbo Han³, Zhengyang Chang⁴, Hao Yu¹, Mingfeng Fan⁵, Yongming Huang⁵, Ruiqing Wang⁶, Sen Li^{1*}, and Shuai Wang^{5*}

¹School of Mental Health, Jining Medical University, Jining, Shandong, China

²Department of Psychology, Affiliated Hospital of Jining Medical University, Jining, Shandong, China

³School of Clinical Medicine, Jining Medical University, Jining, Shandong, China

⁴College of Integrated Traditional Chinese and Western Medicine, Jining Medical University, Jining, Shandong, China

⁵Department of Anorectal Surgery, Affiliated Hospital of Jining Medical University, Jining, Shandong, China

⁶Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Abstract

Constipation, a prevalent gastrointestinal issue, has been linked to neurological health through the gut–brain axis (GBA). This study investigated the genetic association between constipation and white matter (WM) microstructure using a two-sample bidirectional Mendelian randomization (MR) approach. Genetic instruments for constipation were derived from the FinnGen study (41,124 cases and 371,057 controls). Summary statistics for diffusion tensor imaging parameters, including fractional anisotropy (FA) and mean diffusivity (MD), were obtained from the UK Biobank (33,292 subjects). The primary MR analysis used the inverse variance weighted (IVW) method, with supplementary analyses including weighted median, constrained maximum likelihood, and robust adjusted profile score methods. Sensitivity analyses, including Cochran's Q test and MR-Egger regression, assessed heterogeneity and pleiotropy. Two WM imaging-derived phenotypes showed significant causal associations with constipation. Specifically, a higher second MD principal component of the superior longitudinal fasciculus (SLF) showed a significant protective effect against constipation (odds ratio [OR]=0.71, 95% confidence interval [CI]=0.58 – 0.87, $p=7.55\times10^{-4}$). Conversely, higher FA in the anterior corona radiata (ACR) increased constipation risk (OR=1.33, 95% CI=1.11 – 1.60, $p=2.13\times10^{-3}$). No significant causal effect of constipation on WM microstructure was found. All supplementary analyses corroborated the IVW results, indicating robustness and consistency. Sensitivity analyses showed low heterogeneity and no significant directional pleiotropy. This study provides strong evidence for a genetic association between specific WM microstructures and constipation, emphasizing the role of the SLF and ACR in the GBA. These findings highlight the need to consider neurological factors in understanding and managing constipation and warrant further research into the underlying mechanisms and broader implications of the GBA.

Keywords: Constipation; White matter; Diffusion tensor imaging; Mendelian randomization; Gut-brain axis

†These authors contributed equally to this work.

*Corresponding authors:

Shuai Wang
(jyfyws@126.com)
Sen Li
(lisenxr@mail.jnmc.edu.cn)

Citation: Zhou C, Shen H, Ji S, *et al.* causal association between constipation and white matter microstructure: A Mendelian randomization study. *J Clin Basic Psychosom.* 2026;4(1):56-63. doi: 10.36922/JCBP025060010

Received: February 7, 2025

Revised: March 12, 2025

Accepted: May 16, 2025

Published online: June 5, 2025

Copyright: © 2025 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Constipation, characterized by infrequent or difficult bowel movements, is one of the most common gastrointestinal complaints worldwide.¹ While constipation is often perceived as a benign condition, emerging evidence suggests its potential impact on neurological health. Psychological factors, including stress and anxiety, may also influence bowel habits, suggesting a bidirectional relationship between the brain and the gastrointestinal system.² However, the underlying mechanisms linking constipation to these neurological outcomes remain poorly understood. The intricate interplay between gastrointestinal health and neurological function has garnered increasing attention in recent years, particularly to the gut–brain axis (GBA) – a bidirectional communication system.³ This axis governs essential physiological functions and homeostasis, extending beyond conventional organ-specific domains to influence a myriad of bodily processes.^{1,4} Disruption of GBA equilibrium has been implicated in various disorders, including gastrointestinal, psychiatric, and neurological conditions.¹ Understanding the mechanisms underlying this axis is crucial for elucidating the pathophysiology of these disorders and developing targeted interventions.

Diffusion tensor imaging (DTI), a non-invasive neuroimaging technique, enables the characterization of white matter (WM) microstructure in the brain. DTI measures the diffusion of water molecules in brain tissue, providing insights into the organization and integrity of WM tracts.⁵ WM microstructure, composed of axonal fibers and myelin sheaths, plays a crucial role in facilitating communication between brain regions.⁶ Alterations in WM microstructure detected by DTI have been associated with a wide range of neurological conditions, including neurodegenerative diseases, psychiatric disorders, and neurodevelopmental disorders,^{7,8} highlighting its importance as a biomarker of brain health. Besides, DTI has been instrumental in elucidating the neurobiological underpinnings of functional gastrointestinal disorders (FGIDs), such as functional constipation and irritable bowel syndrome (IBS). Studies have demonstrated WM alterations in regions associated with pain processing and emotional regulation among individuals with FGIDs, highlighting the bidirectional influence of gastrointestinal health on brain structure and function.^{9,10} However, the causal relationship between changes in brain structure and the occurrence of these diseases is still unclear.

Recent advances in genetics and neuroimaging have provided valuable tools for investigating the complex interactions within the GBA. Mendelian randomization (MR) is a statistical method that utilizes genetic variants as instrumental variables (IVs) to assess causality in

observational data. By leveraging genetic variants that are randomly allocated at conception and remain fixed throughout life, MR mimics the randomization process in a randomized controlled trial.¹¹ MR studies have gained prominence in elucidating causal relationships in complex traits and diseases, where traditional observational studies are often limited by confounding and reverse causation.^{12,13} MR studies have revealed causal relationships between the digestive system and nervous system, for example, between inflammatory bowel disease and Alzheimer's disease,¹⁴ between IBS and leisure sedentary behavior,¹⁵ and between gut microbiota and multiple sclerosis.¹⁶ However, the application of MR in elucidating causal relationships between constipation and WM microstructure remains limited.

Motivated by the bidirectional nature of the GBA and the potential implications of constipation for neurological outcomes – and recognizing the role of the GBA in the shared genetic etiology of FGIDs and psychiatric conditions¹⁷ – we conducted a two-sample bidirectional MR study to investigate the genetic association between constipation and WM microstructure at a microscopic level. This study aimed to deepen our understanding of the complex interactions between gastrointestinal health and neurological characteristics, with implications for both research and clinical practice.

2. Methods

2.1. MR and the associated assumptions

MR is a method used to assess causal relationships between risk factors and health outcomes using genetic variants as IVs. This approach relies on three core assumptions: (1) Relevance: The genetic variants used as IVs must be associated with the exposure (constipation); (2) Independence: The genetic variants must not be associated with confounders of the exposure-outcome relationship; and (3) Exclusion restriction: the genetic variants must affect the outcome (WM microstructure) only through the exposure and not through alternative pathways. These assumptions help mitigate confounding and reverse causation, making MR a powerful tool for causal inference in epidemiology.

2.2. Data sources and study population

In our study, we obtained summary-level data for constipation from the FinnGen project, which includes 41,124 cases and 371,057 controls. The FinnGen study combines nationwide biobank data with structured national health-care records, leveraging a unique, relatively homogeneous population for robust genetic analysis.¹⁸

For WM microstructure, genome-wide association study (GWAS) summary statistics of DTI parameters were

sourced from the UK Biobank. This dataset encompasses 33,292 subjects and includes measures of fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity, radial diffusivity, mode of anisotropy, mean (averaged parameters), providing a comprehensive characterization of brain WM.¹⁹ Principal component (PC) analysis was applied to the DTI parameters of each WM tract to reduce data dimensionality and extract PCs that capture the most significant sources of variation. The PCs were derived from multiple DTI metrics measured along each tract and ordered according to the amount of variance they explained. These PCs accounted for a considerable proportion of the variance in the corresponding DTI parameters and were mapped onto established WM tracts based on the anatomical localization of the DTI measurements. Detailed information about the DTI parameters and WM tracts used in this study is presented in Supplementary Table S1.

2.3. Selection of IVs

We implemented stringent quality assurance measures, including careful selection and refinement of genetic instruments, comprehensive sensitivity analyses to validate results, and consistent data harmonization and monitoring throughout the analysis phase. IVs were selected based on their strong association with constipation in the GWAS dataset. Single nucleotide polymorphisms (SNPs) reaching genome-wide significance ($p < 5 \times 10^{-8}$) were considered potential IVs. To ensure the relevance assumption of the MR, we applied linkage disequilibrium clumping with a threshold of $r^2 < 0.001$ and a window size of 10,000 kb to ensure independence among the selected SNPs.

2.4. Statistical analysis

The inverse variance weighted (IVW) method²⁰ was utilized as the primary analysis approach to estimate the causal effect of constipation on WM microstructure. This method combines the Wald ratios of individual SNPs to produce an overall estimate of the causal effect. To ensure the robustness of the IVW estimates, additional MR methods, including the weighted median method,¹¹ the constrained maximum likelihood (cML) method,²⁰ and the robust adjusted profile score (RAPS) method,²¹ were employed. A Bonferroni-corrected p -value threshold of 2.38×10^{-3} ($0.05/21$, where 21 represents the number of WM tracts analyzed) was applied to account for multiple comparisons. Cochran's Q test and the I^2 statistic were used to assess heterogeneity among SNP-specific estimates. Evidence of heterogeneity indicates potential violations of MR assumptions due to variability in SNP-specific causal effect estimates.

To detect and account for directional pleiotropy – where genetic variants affect the outcome through pathways

other than the exposure – we conducted MR-Egger regression. A significant intercept ($p < 0.05$) would indicate the presence of directional pleiotropy. All statistical analyses were performed using R software (version – 4.3.0, The R Development Core Team, New Zealand), with the “MendelianRandomization” and “TwoSampleMR” packages.

3. Results

The overall design of the present study is shown in Figure 1. Our results revealed that two WM imaging-derived phenotypes (IDPs) demonstrated significant causal effects on constipation (Figure 2A). Specifically, the MD PC of the superior longitudinal fasciculus (SLF) showed a significant protective effect against constipation. This was evidenced by a 29% reduction in the genetic susceptibility to constipation (IVW method: odds ratio [OR]=0.71, 95% confidence interval [CI]=0.58 – 0.87, $p=7.55 \times 10^{-4}$). This finding indicates that higher MD in this WM tract is associated with a decreased risk of developing constipation. Conversely, the fifth FA PC in the anterior corona radiata (ACR) was found to be associated with an increased risk of constipation. Specifically, higher FA in this region was associated with a 33% increase in the odds of constipation (OR=1.33, 95% CI=1.11 – 1.60, $p=2.13 \times 10^{-3}$) (Figure 2B). This suggests that microstructural alterations in the ACR, as reflected by FA, may contribute to a higher susceptibility to constipation. In contrast, our analysis did not reveal any significant causal effect of constipation on alterations in WM microstructure. This suggests that while specific WM microstructure characteristics can influence the risk of constipation, the reverse – constipation influencing WM microstructure – was not supported by our data.

To ensure the robustness of our primary findings, we performed additional MR analyses using the weighted median, cML, and RAPS methods. These supplementary analyses corroborated the IVW results, indicating the consistency and reliability of the observed associations. Further sensitivity analyses assessed the presence of heterogeneity and pleiotropy. Cochran's Q test and I^2 statistic indicated low heterogeneity among the SNPs used in the IVW estimates, suggesting consistent causal estimates across SNPs. In addition, MR-Egger regression did not show significant evidence of directional pleiotropy, as the intercepts were not significantly different from zero ($p > 0.05$).

The leave-one-out analyses confirmed that no individual SNP significantly dominated the causality estimates. Further scrutiny using scatter plots, funnel plots, and forest plots revealed no considerable heterogeneity (Supplementary Figures S1 and S2).

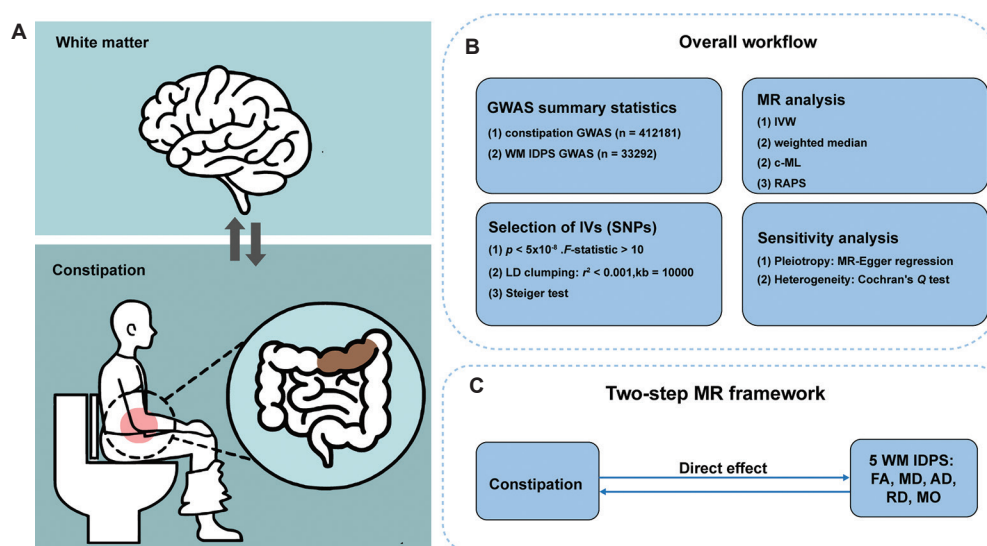


Figure 1. Overview of the study design and analysis. (A) Schematic illustration of the bidirectional relationship between constipation and WM microstructure. (B) Analytical workflow of the MR analysis. (C) The two-sample MR analysis framework, evaluating the direct causal effect of constipation on five WM IDPs.

Abbreviations: ACR: Anterior corona radiata; AD: Axial diffusivity; cML: Constrained maximum likelihood; DTI: Diffusion tensor imaging; FA: Fractional anisotropy; GWAS: Genome-wide association study; IDP: Imaging-derived phenotype; IV: Instrumental variable; IVW: Inverse variance weighted; LD: Linkage disequilibrium; MD: Mean diffusivity; MO: Mode of anisotropy; MR: Mendelian randomization; RAPS: Robust adjusted profile score; RD: Radial diffusivity; SLF: Superior longitudinal fasciculus; SNP: Single-nucleotide polymorphism; WM: White matter.

4. Discussion

Our study provides significant insights into the genetic associations between constipation and specific WM microstructures. The identified WM tracts, such as the SLF and ACR, are frequently implicated in advanced brain functions such as cognition, emotion, and behavior.²² The utilization of DTI measures such as MD and FA to evaluate WM integrity highlights the intricate interplay between brain structure and gastrointestinal health.²³

The SLF is a prominent WM tract connecting the frontal, parietal, and occipital lobes, playing a critical role in various cognitive processes, including language, attention, and working memory.²⁴ Our findings reveal that higher MD in the SLF is associated with a reduced genetic susceptibility to constipation. MD reflects the rate of water diffusion within tissue and provides an index of microstructural integrity.²⁵ An increased MD in the SLF may indicate a healthier WM microstructure, potentially enhancing coordination of GBA signaling pathways, and thereby reducing the risk of constipation. Conversely, the ACR, a tract involved in emotional regulation and executive functions, showed an increased risk of constipation in individuals with higher FA values. FA measures the directional coherence of water diffusion, indicating the integrity and density of WM fibers.²⁶ The observed association between higher FA in the ACR and increased constipation risk suggests that microstructural

alterations in this region could disrupt normal gut-brain communication, leading to gastrointestinal dysfunction. This finding aligns with previous research highlighting the role of the ACR in emotional and autonomic regulation, both of which are crucial for maintaining gut motility.²⁷ The SLF and ACR may influence autonomic and enteric nervous system functions through their connections with brain regions involved in emotional and cognitive processing. These pathways are essential for regulating gut-brain communication and gastrointestinal regulation. Potential mechanisms underlying the observed associations include modulation of autonomic pathways, stress-related or emotional regulation via fronto-limbic circuits, neuroinflammation, and variations in vagal tone. For instance, the SLF's role in cognitive processes could affect autonomic regulation of the gut, while the ACR's involvement in emotional regulation might impact gut motility through fronto-limbic circuits. Neuroinflammatory processes and variations in vagal tone may further mediate the bidirectional communication of GBA, potentially explaining the genetic associations we identified.

The GBA is a complex bidirectional communication network that links the enteric and central nervous systems through hormonal, immunological, and neural pathways.⁴ Our results highlight the importance of this axis in the pathophysiology of constipation. The involvement of specific WM tracts in influencing constipation risk

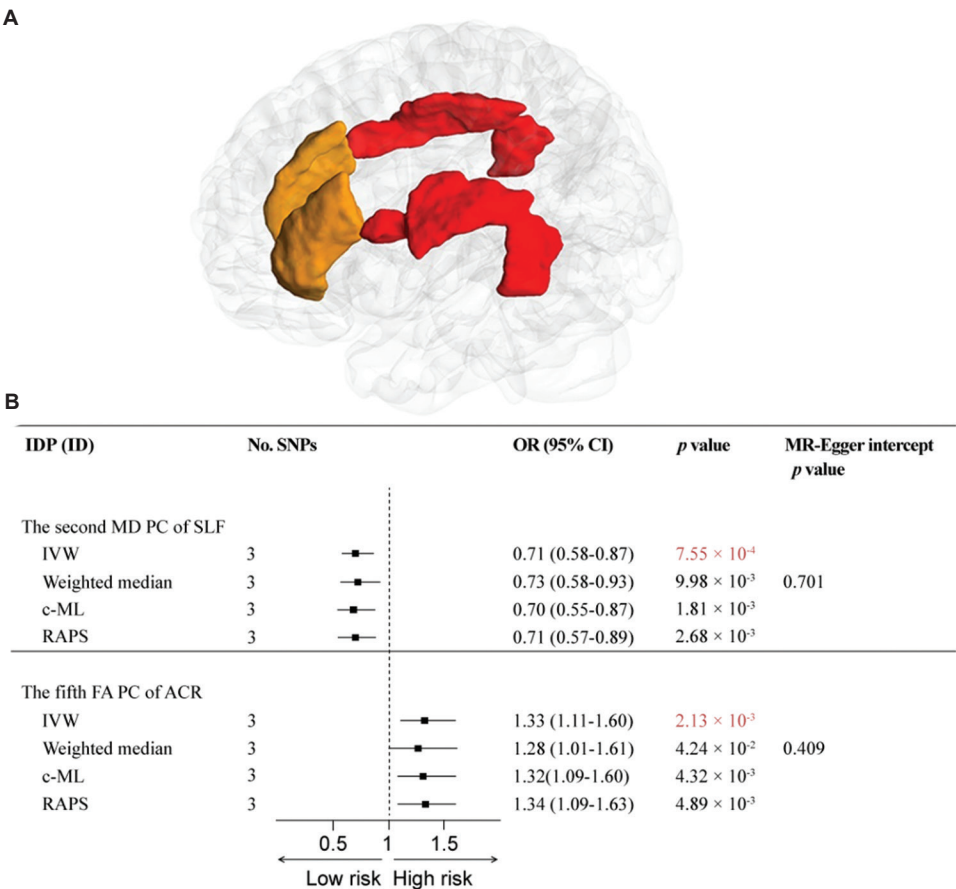


Figure 2. (A) Anatomical locations of the regional WM microstructure show significant causal associations with constipation in the primary MR analysis. SLF is shown in red and ACR is shown in orange. (B) Forest plots exhibiting the causal estimates with ORs and their corresponding 95% CIs are shown on the x-axis. Significant causal correlations ($p < 2.38 \times 10^{-3}$ after Bonferroni correction) are highlighted in red. MR analyses were conducted -using IVW, weighted median, cML, and RAPS methods.

Abbreviations: ACR: Anterior corona radiata; CI: confidence interval; c-ML: Constrained maximum likelihood; FA: Fractional anisotropy; IDP: Imaging-derived phenotype; IVW: Inverse variance weighted; MD: Mean diffusivity; MR: Mendelian randomization; OR: Odds ratio; PC: Principal component; RAPS: Robust adjusted profile score; SLF: Superior longitudinal fasciculus; SNP: Single nucleotide polymorphism; WM: White matter.

underscores the need for integrated models that consider both the neurological and gastrointestinal dimensions of this condition. Given the bidirectional nature of the GBA, gastrointestinal disturbances such as constipation can lead to alterations in brain structure and function, while neurological changes can impact gut motility and function.^{3,28} This interplay suggests that interventions targeting one component of the GBA may have profound effects on the other, highlighting the potential for holistic treatment approaches.¹

The findings of our MR study carry several important clinical and research implications. First, they suggest that targeting WM microstructure may serve as a novel therapeutic approach for managing constipation. For example, interventions aimed at enhancing the integrity of the SLF could potentially reduce constipation risk. In addition, understanding the genetic basis of these

associations could inform personalized medicine strategies, where individuals at high genetic risk of constipation could receive targeted interventions to prevent or manage the condition.^{29,30} Further research is necessary to validate our findings and explore the underlying mechanisms linking WM microstructure and constipation. Longitudinal studies tracking changes in WM integrity alongside constipation onset and progression would be particularly valuable. Moreover, exploring the role of other WM tracts and their interactions within the broader GBA could provide deeper insights into the systemic nature of these associations.^{3,17} The application of advanced neuroimaging techniques, such as DTI, in larger and more diverse populations will enhance the generalizability of our findings.^{31,32} In addition, integrating neuroimaging data with other omics approaches, such as genomics, proteomics, and metabolomics, could offer a more comprehensive

understanding of the biological pathways involved.^{33,34} Future studies may also benefit from implementing region-specific imaging analyses to more precisely delineate the relationship between WM alterations and constipation. Our findings pave the way for exploring behavioral or neuromodulatory interventions targeting WM structures such as the SLF and ACR. Potential approaches may include stress management techniques, cognitive-behavioral therapies, or non-invasive electrical neuromodulation methods aimed at improving gut-brain communication and reducing constipation risk.

Despite providing novel insights, our study has several limitations. The use of summary-level data in MR analyses limits our ability to explore more nuanced relationships between specific genetic variants and WM microstructure. Future investigations using individual-level data could provide a more detailed understanding of the genetic architecture underlying these associations. Moreover, although MR is a powerful tool for causal inference, it depends on several core assumptions. Violations of these assumptions, particularly the presence of horizontal pleiotropy – where genetic variants influence the outcome through pathways independent of the exposure – could bias our results. Although we employed methods such as MR-Egger regression to detect and account for pleiotropy, these methods have their own limitations. Future studies should also consider the potential impact of environmental and lifestyle factors on the GVA. Factors such as diet, physical activity, stress, and medication use are known to influence both gastrointestinal and neurological health. These factors may interact with genetic predispositions to modulate the risk of constipation. Understanding these interactions could help in developing more effective and personalized treatment strategies. Last but not least, our samples were restricted to individuals from the European population, which may limit the generalizability of our findings to other populations. Replication studies in more diverse cohorts are needed to confirm the relevance of these associations across different ethnic groups.

5. Conclusion

This MR study provides robust evidence for a genetic association between specific WM microstructures and constipation. The involvement of WM tracts, such as the SLF and ACR, highlights the complex interplay between brain and gut health. These findings underscore the importance of considering both neurological and gastrointestinal factors in understanding and managing constipation. Future research should focus on validating these findings, exploring the underlying mechanisms, and

considering the broader context of the GBA to develop comprehensive and effective therapeutic approaches.

Acknowledgments

None.

Funding

This research was funded by the Medical and Health Science and Technology Development Plan of Shandong Province (Grant No.: 202003061210 and 202304011343), the Key Research and Development Plan of Jining City (Grant No.: 2021YXNS024 and 2023JNZC141), the Cultivation Plan of High-level Scientific Research Projects of Jining Medical University (Grant No.: JYGC2021KJ006), the Ministry of Education's Industry School Cooperation Collaborative Education Project (Grant No.: 220900242232529), the National Natural Science Foundation of China (81901358), the Natural Science Foundation of Shandong Province (Grant No.: ZR2019BH001 and ZR2021YQ55), the Young Taishan Scholars of Shandong Province (Grant No.: tsqn201909146), and the Supporting Fund for Teachers' Research of Jining Medical University (Grant No.: 600903001).

Conflict of interest

The authors declare no competing interests.

Author contributions

Conceptualization: Cong Zhou, Hao Yu, Chuanxin Liu, Shuai Wang

Data curation: Sen Li, Shanling Ji, Shengbo Han, Zhengyang Chang, Mingfeng Fan, Yongming Huang

Formal analysis: Ruiqing Wang

Funding acquisition: Hao Yu, Shuai Wang

Investigation: Cong Zhou

Methodology: Sen Li, Shanling Ji, Ruiqing Wang, Shengbo Han, Zhengyang Chang, Mingfeng Fan, Yongming Huang

Project administration: Shuai Wang

Resources: Cong Zhou, Hao Yu, Chuanxin Liu

Software: Sen Li, Shanling Ji, Shengbo Han, Zhengyang Chang

Supervision: Hao Yu, Chuanxin Liu, Shuai Wang

Validation: Cong Zhou, Ruiqing Wang, Hao Yu, Chuanxin Liu, Shuai Wang

Visualization: Ruiqing Wang, Sen Li, Shanling Ji, Shengbo Han, Zhengyang Chang, Mingfeng Fan, Yongming Huang

Writing – original draft: Cong Zhou, Ruiqing Wang

Writing – review & editing: Cong Zhou, Sen Li, Shanling Ji, Shengbo Han, Zhengyang Chang, Hao Yu, Chuanxin Liu, Mingfeng Fan, Yongming Huang, Shuai Wang

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

All data are publicly available. The data sources for this study include the FinnGen consortium (<https://r10.finnngen.fi/>) and BIG-S2 (<https://www.med.unc.edu/bigs2/data/gwas-summary-statistics/>).

Further disclosure

Part of the findings have been presented at the 30th Annual Conference of the Psychosomatic Medicine Branch of the Chinese Medical Association in Fuzhou, China.

References

1. Morais LH, Schreiber HL 4th, Mazmanian S. The gut microbiota-brain axis in behaviour and brain disorders. *Nat Rev Microbiol*. 2021;19(4):241-255.
doi: 10.1038/s41579-020-00460-0
2. Black CJ, Drossman DA, Talley NJ, Ruddy J, Ford AC. Functional gastrointestinal disorders: Advances in understanding and management. *Lancet*. 2020;396(10263):1664-1674.
doi: 10.1016/s0140-6736(20)32115-2
3. Mayer EA, Nance K, Chen S. The gut-brain axis. *Annu Rev Med*. 2022;73(1):439-453.
doi: 10.1146/annurev-med-042320-014032
4. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol*. 2015;28(2):203-209.
5. Le Bihan D, Mangin JF, Poupon C, *et al*. Diffusion tensor imaging: Concepts and applications. *J Magn Reson Imaging*. 2001;13(4):534-546.
doi: 10.1002/jmri.1076
6. Lebel C, Deoni S. The development of brain white matter microstructure. *Neuroimage*. 2018;182:207-218.
doi: 10.1016/j.neuroimage.2017.12.097
7. Setiadi TM, Martens S, Opmeer EM, *et al*. Widespread white matter aberration is associated with the severity of apathy in amnesic mild cognitive impairment: Tract-based spatial statistics analysis. *Neuroimage Clin*. 2021;29:102567.
doi: 10.1016/j.nicl.2021.102567
8. Mitelman SA. Transdiagnostic neuroimaging in psychiatry: A review. *Psychiatry Res*. 2019;277:23-38.
doi: 10.1016/j.psychres.2019.01.026
9. Ellingson BM, Mayer E, Harris RJ, *et al*. Diffusion tensor imaging detects microstructural reorganization in the brain associated with chronic irritable bowel syndrome. *Pain*. 2013;154(9):1528-1541.
doi: 10.1016/j.pain.2013.04.010
10. Hu Y, Jia Z, Zhang L, *et al*. White-matter microstructural alterations in patients with functional constipation: A tract-based spatial statistics study. *Neurogastroenterol Motil*. 2022;34(5):e14338.
doi: 10.1111/nmo.14338
11. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol*. 2016;40(4):304-314.
doi: 10.1002/gepi.21965
12. Smith GD, Ebrahim S. 'Mendelian randomization': Can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol*. 2003;32(1):1-22.
doi: 10.1093/ije/dyg070
13. Davey Smith G, Hemani G. Mendelian randomization: Genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet*. 2014;23:R89-R98.
doi: 10.1093/hmg/ddu328
14. Jiang L, Li JC, Shen L, Tang BS, Guo JF. Association between inflammatory bowel disease and Alzheimer's disease: Multivariable and bidirectional Mendelian randomisation analyses. *Gut*. 2023;72(9):1797-1799.
doi: 10.1136/gutjnl-2022-327860
15. Lu L, Liu C, Liu K, *et al*. The causal effects of leisure screen time on irritable bowel syndrome risk from a Mendelian randomization study. *Sci Rep*. 2023;13(1):13216.
doi: 10.1038/s41598-023-40153-1
16. Sun D, Zhang Y, Wang R, *et al*. Causal effects of gut microbiota on multiple sclerosis: A two-sample mendelian randomization study. *Brain Behav*. 2024;14(6):e3593.
doi: 10.1002/brb3.3593
17. Gong W, Guo P, Li Y, *et al*. Role of the gut-brain axis in the shared genetic etiology between gastrointestinal tract diseases and psychiatric disorders: A genome-wide pleiotropic analysis. *JAMA Psychiatry*. 2023;80(4):360-370.
doi: 10.1001/jamapsychiatry.2022.4974
18. Kurki MI, Karjalainen J, Palta P, *et al*. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature*. 2023;613(7944):508-518.
doi: 10.1038/s41586-022-05473-8
19. Zhao B, Li T, Yang Y, *et al*. Common genetic variation

- influencing human white matter microstructure. *Science*. 2021;372(6548):eabf3736.
doi: 10.1126/science.abf3736
20. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol*. 2013;37(7):658-665.
doi: 10.1002/gepi.21758
21. Slob EAW, Burgess S. A comparison of robust mendelian randomization methods using summary data. *Genet Epidemiol*. 2020;44(4):313-329.
doi: 10.1002/gepi.22295
22. Douglas Fields R. White matter in learning, cognition and psychiatric disorders. *Trends Neurosci*. 2008;31(7):361-370.
doi: 10.1016/j.tins.2008.04.001
23. Peter JB, Derek KJ. Diffusion-tensor MRI: Theory, experimental design and data analysis - a technical review. *NMR Biomed*. 2002;15:456-467.
doi: 10.1002/nbm.783
24. Nakajima R, Kinoshita M, Shinohara H, Nakada M. The superior longitudinal fascicle: reconsidering the fronto-parietal neural network based on anatomy and function. *Brain Imaging Behav*. 2020;14(6):2817-2830.
doi: 10.1007/s11682-019-00187-4
25. Wassenaar TM, Yaffe K, Van Der Werf YD, Sexton CE. Associations between modifiable risk factors and white matter of the aging brain: Insights from diffusion tensor imaging studies. *Neurobiol Aging*. 2019;80:56-70.
doi: 10.1016/j.neurobiolaging.2019.04.006
26. Sanjuan PM, Thoma R, Claus ED, Mays N, Caprihan A. Reduced white matter integrity in the cingulum and anterior corona radiata in posttraumatic stress disorder in male combat veterans: A diffusion tensor imaging study. *Psychiatry Res*. 2013;214(3):260-268.
doi: 10.1016/j.psychresns.2013.09.002
27. Burke T, Holleran L, Mothersill D, *et al*. Bilateral anterior corona *radiata* microstructure organisation relates to impaired social cognition in schizophrenia. *Schizophr Res*. 2023;262:87-94.
doi: 10.1016/j.schres.2023.10.035
28. Aburto MR, Cryan JF. Gastrointestinal and brain barriers: Unlocking gates of communication across the microbiota-gut-brain axis. *Nat Rev Gastroenterol Hepatol*. 2024;21(4):222-247.
doi: 10.1038/s41575-023-00890-0
29. McCarthy MI, Abecasis GR, Cardon LR, *et al*. Genome-wide association studies for complex traits: Consensus, uncertainty and challenges. *Nat Rev Genet*. 2008;9(5):356-369.
doi: 10.1038/nrg2344
30. Ting Q, Liyang S, Yazhou G, Chang C, Jian Y. From genetic associations to genes: Methods, applications, and challenges. *Trends Genet*. 2024;40:642-667.
doi: 10.1016/j.tig.2024.04.008
31. Zhao B, Zhang J, Ibrahim JG, *et al*. Large-scale GWAS reveals genetic architecture of brain white matter microstructure and genetic overlap with cognitive and mental health traits (n = 17,706). *Mol Psychiatry*. 2021;26(8):3943-3955.
doi: 10.1038/s41380-019-0569-z
32. Tae WS, Ham BJ, Pyun SB, Kang SH, Kim BJ. Current clinical applications of diffusion-tensor imaging in neurological disorders. *J Clin Neurol*. 2018;14(2):129-140.
doi: 10.3988/jcn.2018.14.2.129
33. Konrad JK, Snyder MP. Integrative omics for health and disease. *Nat Rev Genet*. 2018;19(5):299-310.
doi: 10.1038/nrg.2018.4
34. Lan L, Feng K, Wu Y, *et al*. Phenomic imaging. *Phenomics*. 2024;3(6):1-16.
doi: 10.1007/s43657-023-00128-8