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ORIGINAL RESEARCH ARTICLE

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

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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=7.55×10^{-4}). Conversely, higher FA in the anterior corona radiata (ACR) increased constipation risk (OR=1.33, 95% CI=1.11 – 1.60, p=2.13×10^{-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

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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 conditions[17] — 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 ($p<5\times10^{-8}$) 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) method[20] 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, $p=7.55\times10^{-4}$). 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, $p=2.13\times10^{-3}$) (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).

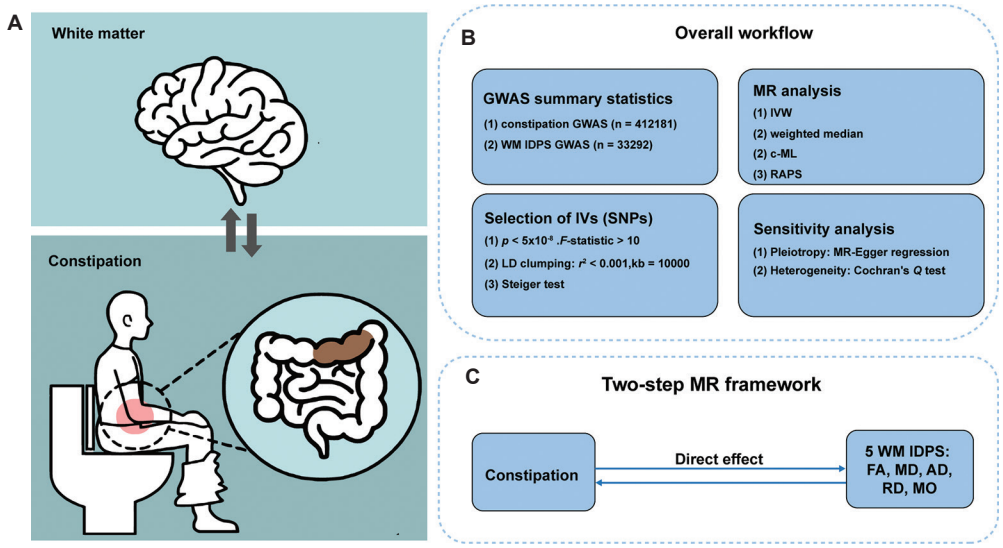


Figure 1. Overview of the study design and analysis. (A) Schematic illustration of the bidirectional relationship between constipation and WM microstructure. (B) Analytical workflow of the MR analysis. (C) The two-sample MR analysis framework, evaluating the direct causal effect of constipation on five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

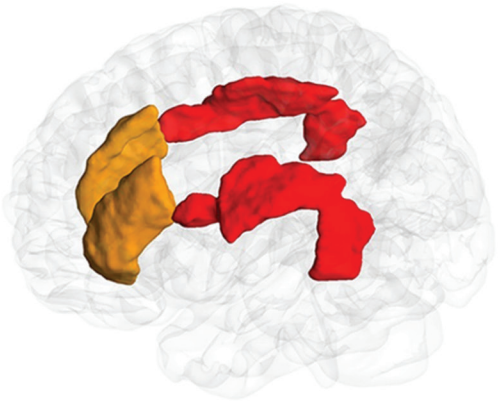
4. Discussion

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

A



B

IDP (ID)	No. SNPs	OR (95% CI)	*p* value	MR-Egger intercept *p* value
The second MD PC of SLF				
IVW	3	0.71 (0.58-0.87)	7.55×10^{-4}	
Weighted median	3	0.73 (0.58-0.93)	9.98×10^{-3}	0.701
c-ML	3	0.70 (0.55-0.87)	1.81×10^{-3}	
RAPS	3	0.71 (0.57-0.89)	2.68×10^{-3}	
The fifth FA PC of ACR				
IVW	3	1.33 (1.11-1.60)	2.13×10^{-3}	
Weighted median	3	1.28 (1.01-1.61)	4.24×10^{-2}	0.409
c-ML	3	1.32(1.09-1.60)	4.32×10^{-3}	
RAPS	3	1.34 (1.09-1.63)	4.89×10^{-3}	

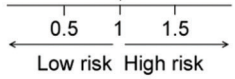


Figure 2. (A) Anatomical locations of the regional WM microstructure show significant causal associations with constipation in the primary MR analysis. SLF is shown in red and ACR is shown in orange. (B) Forest plots exhibiting the causal estimates with ORs and their corresponding 95% CIs are shown on the x-axis. Significant causal correlations ($p<2.38\times10^{-3}$ 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.

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Conflict of interest

The authors declare no competing interests.

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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.finngen.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.

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