

Exploring the Impact of Constipation on Mental Health and Non-Motor Symptoms in Parkinson's Disease Patients: A Clinical and Mendelian Randomization Approach

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ABSTRACT

Background & Aims: Parkinson's disease (PD) patients frequently experience constipation and non-motor symptoms, significantly affecting their quality of life. Although constipation is common, its causal relationship with mental health issues, such as anxiety and depression, remains underexplored. This study aims to investigate the association between constipation severity, non-motor symptoms, and mental health outcomes in PD patients.

Methods: A total of 97 PD patients from three hospitals in Changshu City were included in this study. Clinical data were collected using assessment tools, including the Non-Motor Symptoms Scale, Patient Assessment of Constipation Quality of Life questionnaire, Hamilton Depression Rating Scale, and Hamilton Anxiety Rating Scale. Mendelian randomization analysis was applied to examine the causal relationships between constipation severity, non-motor symptoms, and mental health outcomes.

Results: A moderate correlation was found between constipation severity and non-motor symptoms, especially in elderly and female patients. However, no significant causal association was identified between constipation and mental health issues such as anxiety, depression, or sleep disorders.

Conclusions: The study underscores the importance of managing constipation in PD patients to improve their non-motor symptoms and quality of life. Despite the observed correlation with non-motor symptoms, further studies are needed to clarify the role of constipation in mental health issues in PD.

Key words: Parkinson's disease – constipation – non-motor symptoms – mental health – Mendelian randomization – quality of life.

Abbreviations: PD: Parkinson's disease; HARS: Hamilton Anxiety Rating Scale; HDRS: Hamilton Depression Rating Scale; MR: Mendelian randomization; NMSS: Non-Motor Symptoms Scale; PAC-QOL: Patient Assessment of Constipation Quality of Life; SCOPA-AUT: Scales for Outcomes in Parkinson's Disease – Autonomic.

INTRODUCTION

Parkinson's disease (PD) is a progressively degenerative neurological disorder predominantly affecting the elderly [1-3]. According to the World Health Organization, approximately 10 million individuals worldwide are affected by this disease [4, 5]. The hallmark symptoms of PD include muscle rigidity, tremors, bradykinesia, and impaired balance [6-8]. Beyond these motor symptoms, non-motor symptoms

significantly deteriorate the quality of life, encompassing sleep disorders, emotional disturbances, and autonomic dysfunction [9]. Among these, constipation, a prevalent autonomic dysfunction, not only disrupts daily activities but may also be linked to the psychological health and other non-motor symptoms of patients [10]. Although constipation is commonly observed in patients with PD, further research is needed to elucidate its exact pathophysiology and impact [6, 11, 12].

Recent studies have highlighted that constipation in PD patients may involve complex neurological mechanisms, including degeneration of dopaminergic neurons in the enteric nervous system and central autonomic dysfunction. Additionally, dopaminergic and anticholinergic medications commonly used in PD treatment significantly contribute to gastrointestinal dysmotility, exacerbating constipation symptoms [13-15].

Constipation is the most frequent gastrointestinal symptom in PD and a significant factor affecting the patient's quality of life [6, 16, 11]. Studies indicate that between 40% and 80% of patients with PD experience constipation, exacerbating physical discomfort, and potentially increasing psychological stress [6, 16, 11]. Moreover, the severity of constipation has been linked to increased levels of depression, anxiety, and decreased sleep quality in numerous studies [17-19]. However, these are observational studies, and their results are susceptible to various confounding factors, making it challenging to establish causal relationships. Therefore, exploring the causal links between constipation, psychological health, and sleep disorders is crucial for a comprehensive understanding of the pathophysiological characteristics of PD and its management strategies.

Mendelian randomization (MR) offers a novel research approach to explore this issue further. This method uses genetic variants as instrumental variables, aiding researchers in clarifying causal relationships that are elusive in observational studies. By utilizing this approach, researchers can more effectively differentiate between causation and mere association, thereby providing more precise strategies for disease management. MR has been extensively applied in recent medical research for the etiology of various diseases, particularly in complex conditions such as PD, where its value is especially prominent [20-22].

Despite existing studies providing evidence of a link between constipation and the mental health and sleep disorders of patients with PD, these studies have significant limitations. For instance, inadequate sample sizes, study design biases, and data processing inconsistencies can all impact the accuracy and generalizability of the results. Moreover, variations in lifestyle habits, cultural backgrounds, and medical conditions across different regions and populations may contribute to heterogeneity in research outcomes. Therefore, addressing this scientific issue urgently requires adopting uniform and rigorous research designs, utilizing advanced statistical methods and analytical tools to profoundly investigate the causal relationships between constipation and mental health and sleep disorders in patients with PD.

This study, based on samples from patients with PD at three hospitals in Changshu, China, employs MR analysis to evaluate the associations and causal relationships between the severity of constipation and non-motor symptoms, autonomic function, quality of life, anxiety, and depression. Through this research, we aim to provide a scientific foundation for comprehensive management and personalized treatment of PD, particularly in enhancing overall quality of life through improved gastrointestinal function. Additionally, the findings of this study will contribute to advancing research in related fields and provide valuable insights for developing new treatment strategies and interventions.

METHODS

Study Participants

All participants diagnosed with constipation-related PD were recruited from three hospitals in Changshu City: the Changshu Fifth People's Hospital, Changshu Hospital of Traditional

Chinese Medicine, and Changshu Second People's Hospital. Experienced neurologists diagnosed these patients between January and August 2023. The study received ethical approval from the ethics committee of the Changshu Fifth People's Hospital (Ethics Approval No.: 2022 LUN Review [Application] Batch 6). Ethical approval for this observational study was also granted by the ethics committees of all three hospitals, and informed consent was obtained from all participants.

Inclusion and Exclusion Criteria

Inclusion criteria were: 1) all participants must be diagnosed with PD, conforming to the established diagnostic criteria for PD, as confirmed by a neurologist; 2) participants must meet the Rome IV diagnostic criteria for constipation, which include at least two of the following symptoms: reduced frequency of defecation, hard stools, difficulty defecating, a sensation of incomplete evacuation, or anorectal obstruction; 3) participants must have a Hoehn-Yahr stage of 5 or less; 4) all participants must voluntarily join the study and sign an informed consent form.

Exclusion criteria were: 1) individuals with cognitive impairments, psychiatric disorders, severe depression, hearing impairments, or other conditions that prevent cooperation with examinations and treatments; 2) severe impairment of organ function, such as cardiac, hepatic, or renal disorders, or serious life-threatening conditions like severe cardiovascular diseases or malignant tumors; 3) history of anorectal surgery, including anal resection or the presence of anorectal tumors, deformities, or intestinal obstructions; 4) secondary Parkinsonism or Parkinson-plus syndromes; 5) poor compliance or other reasons that lead to non-cooperation with the study protocol (Fig. 1).

Assessment Methods

A neurologist conducted a questionnaire survey for all patients and recorded demographic information, such as gender, age, education level, disease duration, and medical history, through face-to-face interviews (All questionnaire information can be found in Supplementary Tables). All enrolled patients met the movement disorder diagnostic criteria proposed by the Movement Disorder Society (MDS) [23] and the Rome IV criteria [24]. The Wexner score was used to assess the severity of constipation [25]. In addition to the Wexner constipation scoring scale, we also recorded the usage and frequency of laxatives or suppositories among patients as supplementary indicators to further evaluate the severity of constipation, providing a more comprehensive assessment of constipation severity and treatment burden. The severity of Non-Motor Symptoms Scale (NMSS) was estimated for all patients [26], with the gastrointestinal, urinary, cardiovascular, and sexual symptom subdomains of NMSS related to autonomic function [27]. Patient Assessment of Constipation Quality of Life (PAC-QOL) questionnaire was used to assess the impact of constipation on quality of life [28], comprising 28 items divided into four dimensions (worry/concern, physical discomfort, psychosocial discomfort, and satisfaction) [29]. Anxiety was assessed using the 14-item Hamilton Anxiety Rating Scale (HARS). A score ≥ 7 indicated anxiety or depression [30].

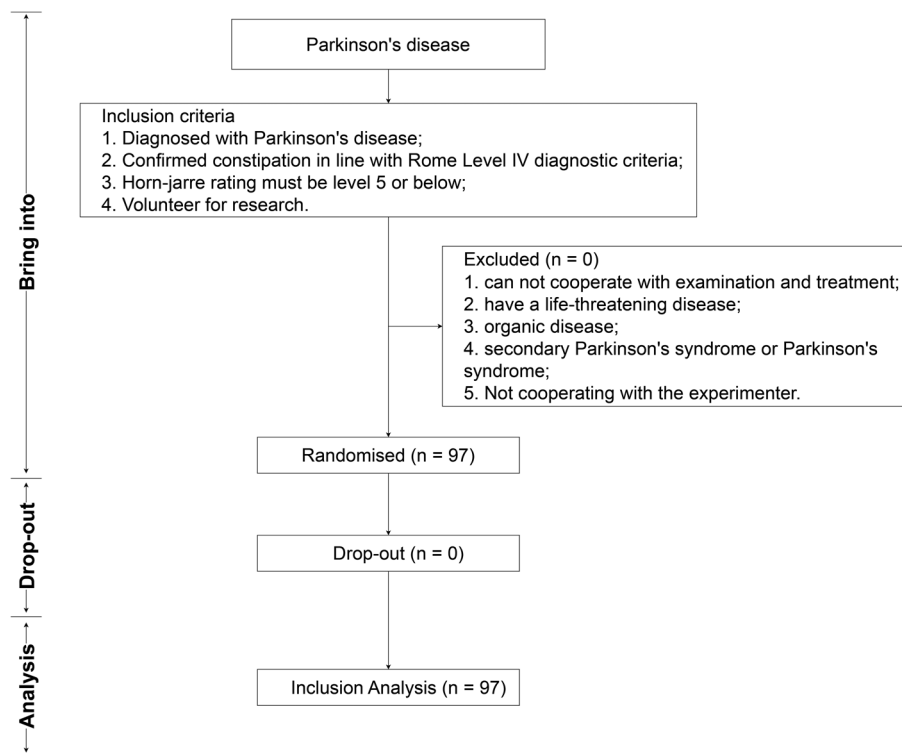


Fig. 1. Patient inclusion and exclusion flowchart.

In addition, this study collected information on the use of anti-Parkinson's disease medications for all participants, including levodopa, dopamine agonists, COMT inhibitors, anticholinergic drugs, and others, and assessed their potential impact on constipation. Data on medication use have been included in the supplementary materials to provide more detailed information on participants' medication exposure (Supplementary file).

Data Acquisition for Mendelian Randomization Analysis

To investigate the causal relationships between the severity of constipation and various factors such as non-motor symptoms, autonomic function, quality of life, anxiety, and depression, this study employed MR analysis. Initially, genetic variation data related to constipation and associated symptoms were collected to serve as instrumental variables for the analysis. The IEU OpenGWAS database (<https://gwas.mrcieu.ac.uk/>) was accessed using keywords such as "Constipation," "Parkinson's Disease," "Non-Motor Symptoms," "Autonomic Function," "Anxiety," and "Depression." These searches identified GWAS studies significantly associated with

the severity of constipation and its related symptoms, providing the necessary genetic variation data.

After extensive searching and filtering, no datasets related to non-motor symptoms or autonomic function were retrieved. Consequently, this study selected the dataset "Diagnoses - main ICD10: K59.0 Constipation (Dataset: ukb-b-6779)" as the exposure dataset. The outcome datasets are "Anxiety or panic attacks (Dataset: ebi-a-GCST90038651)" for anxiety, "Depression (Dataset: ebi-a-GCST90038650)" for depression, and "Sleep disorders (combined) (Dataset: ukb-d-SLEEP)" for sleep disorders (Table I). These datasets include samples from both male and female European populations. The constipation dataset comprises 463,010 samples with 9,851,867 single nucleotide polymorphisms (SNPs); the anxiety dataset includes 484,598 samples with 9,587,836 SNPs; the depression dataset also includes 484,598 samples but with the same number of SNPs; and the sleep disorders dataset contains 361,194 samples with 11,120,383 SNPs. The comprehensive nature of these datasets provides the conditions for high-quality MR analysis, facilitating an in-depth understanding of the causal relationships between these biomarkers and the severity of ICP.

Table I. Expose data and outcome data details

Data set	Year	Population	Sample size	Number of SNPs	Author
Diagnoses - main ICD10: K59.0 Constipation	2018	European	463010	9851867	Ben Elsworth
Anxiety or panic attacks	2021	NA	484598	9587836	D<U+00F6>nerta<U+015F> HM
Depression	2021	NA	484598	9587836	D<U+00F6>nerta<U+015F> HM
Sleep disorders (combined)	2018	European	361194	11120383	Neale lab

SNP: single nucleotide polymorphism.

Selection and Application of Instrumental Variables

This study employs MR analysis to identify genetic instrumental variables associated with the severity of constipation and related non-motor symptoms, such as autonomic function, quality of life, anxiety, and depression. The severity of these symptoms is influenced by genetic factors, disease progression, lifestyle habits, and psychological state. When investigating the causal relationships between the severity of constipation, non-motor symptoms, and autonomic function, it is crucial to consider these factors as potential confounders.

During the GWAS analysis, a statistical significance threshold of $p < 5 \times 10^{-8}$ is used to identify SNPs significantly associated with the severity of constipation and its related symptoms. To ensure the independence of selected SNPs, we consider a linkage disequilibrium threshold ($r^2 < 0.01$). Additionally, appropriate genomic region widths are set to minimize the influence of pleiotropy on the analysis results. This approach ensures the selection of reliable instrumental variables directly related to the severity of constipation and its associated symptoms.

Multi-Method Mendelian Randomization Analysis

To explore the causal relationships between the severity of constipation and factors such as non-motor symptoms, autonomic function, quality of life, anxiety, and depression, this study conducted MR analysis using multiple methods. Specifically, the data was used to analyze five regression models - MR-Egger regression, the weighted median estimator (WME), the inverse-variance weighted (IVW) method, the simple mode method, and the weighted mode method. The results were visually represented through graphical displays. These methods validated the causal links between the severity of constipation and various related non-motor symptoms.

Statistical Analysis

Statistical analyses were conducted using R version 4.0.3 (R Foundation). Essential characteristics of patients were expressed as means with standard deviations (SD) or frequencies with percentages, as appropriate. Patients were categorized by age (< 65 and ≥ 65 years) and gender. The Kruskal-Wallis or χ^2 tests were utilized to assess group characteristics differences. Spearman correlation analysis was performed to examine the relationships between Wexner constipation scores, the NMSS, the Scales for Outcomes in Parkinson's Disease - Autonomic (SCOPA-AUT), the PAC-QOL, the Hamilton Depression Rating Scale (HDRS), and the HARS scores. Univariate and multivariate linear regression analyses were conducted to evaluate the associations between autonomic function scores and Wexner constipation scores. The multivariate models were adjusted for age, gender, disease duration, family history, educational level, and Hoehn-Yahr staging, selecting covariates based on prior knowledge and baseline characteristics of the study participants that could influence the prognosis of constipation in PD.

Mendelian randomization studies were performed using the "TwoSampleMR" and "MRPRESSO" packages in R software version 4.3.2 to ensure the accuracy and reliability of the results. Detailed tests for heterogeneity and pleiotropy were conducted, along with a leave-one-out approach, to assess the sensitivity

of the analysis. A p -value of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

This study included 97 PD patients with constipation (Tables II and III, Fig 1). Among the 97 participants, 68 individuals (70.1%) were using levodopa, 41 (42.3%) were using dopamine agonists, and 26 (26.8%) were using anticholinergic drugs. Statistical analysis revealed that patients using anticholinergic drugs had significantly higher Wexner constipation scores compared to those who did not use these medications ($p=0.018$), suggesting that anticholinergic drugs may exacerbate constipation symptoms. Additionally, patients using dopamine agonists exhibited higher autonomic dysfunction in the SCOPA-AUT gastrointestinal subscale ($p=0.042$). These findings indicate that pharmacological treatments may play a significant role in the occurrence and severity of constipation related to Parkinson's disease.

The average age of the participants was 69.12 years ($SD=10.53$), with male patients averaging 71.86 years ($SD=6.88$) and female patients averaging 66.94 years ($SD=12.35$). The age difference between genders was insignificant ($p=0.104$) (Fig. 2A). The average disease duration was 8.36 years ($SD=5.17$), with males averaging 8.05 years ($SD=5.08$) and females 8.61 years ($SD=5.28$), showing no significant difference between genders ($p=0.596$) (Fig. 2B).

Table II. Demographic characteristics of the patients (Updated Version)

Characteristics	Total (N=97)	Male (N=43)	Female (N=54)	p-value
Age (years)	69.12±10.53	71.86±6.88	66.94±12.35	0.104
Disease duration (years)	8.36±5.17	8.05±5.08	8.61±5.28	0.596
Family history, n (%)	14 (14.43)	10 (23.26)	4 (7.41)	0.047
Education level				0.003
Illiterate	19 (19.59)	2 (4.65)	17 (31.48)	
Primary school	24 (24.74)	14 (32.56)	10 (18.52)	
Middle school	42 (43.30)	22 (51.16)	20 (37.04)	
College	12 (12.37)	5 (11.63)	7 (12.96)	
Hoehn-Yahr staging, n (%)				0.821
1	14 (14.43)	5 (11.63)	9 (16.67)	
1.5	11 (11.34)	6 (13.95)	5 (9.26)	
2	16 (16.49)	7 (16.28)	9 (16.67)	
2.5	10 (10.31)	7 (16.28)	3 (5.56)	
3	31 (31.96)	11 (25.58)	20 (37.04)	
4	12 (12.37)	7 (16.28)	5 (9.26)	
5	3 (3.09)	0 (0.00)	3 (5.56)	
Medication use, n (%)				
Levodopa	68 (70.1)	30 (69.8)	38 (70.4)	0.943
Dopamine agonists	41 (42.3)	19 (44.2)	22 (40.7)	0.765
Anticholinergic drugs	26 (26.8)	13 (30.2)	13 (24.1)	0.489

Table III. Demographic characteristics of the younger and older patients

Characteristics ^a	The younger (N=28)	The older (N=69)	p
Male	9 (32.14)	34 (49.28)	0.124
Disease duration, years	7.61±6.31	8.67±4.65	0.223
Family history, n (%)	4 (14.29)	10 (14.49)	0.339
Education			0.002
Illiteracy	2 (7.14)	17 (24.64)	
Primary school	8 (28.57)	16 (23.19)	
Middle school	13 (46.43)	29 (42.03)	
College	5 (17.86)	7 (10.14)	
Hoehn-Yahr staging, n (%)			0.002
1.0	11 (39.29)	3 (4.35)	
1.5	1 (3.57)	10 (14.49)	
2.0	3 (10.71)	13 (18.84)	
2.5	2 (7.14)	8 (11.59)	
3.0	8 (28.57)	23 (33.33)	
4.0	2 (7.14)	10 (14.49)	
5.0	1 (3.57)	2 (2.90)	
NMSS score			
Cardiovascular	3.75±5.19	4.86±6.08	0.271
Sleep/Fatigue	10.79±10.80	13.43±10.50	0.113
Mood/Apathy	14.68±18.05	16.78±16.67	0.259
Perceptual problems/ Hallucinations	4.61±7.70	4.90±7.11	0.204
Attention/Memory	5.21±7.48	6.97±8.69	0.269
Gastrointestinal	5.46±5.29	7.33±7.53	0.321
Urinary	5.71±5.32	7.70±8.63	0.592
Sexual function	3.75±5.59	4.77±7.51	0.513
Others	8.54±9.69	9.46±10.25	0.431
Total scores	62.50±63.20	76.20±67.71	0.184
SCOPA-AUT score			
Gastrointestinal	4.25±3.42	4.67±3.50	0.606
Urinary	4.46±2.96	4.72±3.82	0.990
Cardiovascular	1.54±1.73	2.28±2.06	0.112
Thermoregulatory	2.93±2.57	2.55±2.28	0.564
Pupillomotor	0.79±0.79	0.58±0.76	0.175
Sexual function	1.96±2.76	1.61±2.38	0.433
Total scores	15.93±9.92	16.41±11.20	0.971
Wexner constipation score	8.29±4.40	9.93±5.03	0.178
PAC-QOL score	55.36±19.81	59.04±20.86	0.390
HDRS score	15.43±12.12	15.04±11.49	0.978
HARS score	12.61±10.95	14.28±10.55	0.351

NMSS: non-motor symptom assessment scale for Parkinson's disease; SCOPA-AUT: scales for outcomes in Parkinson's disease-autonomic; PAC-QOL: patient assessment of constipation quality of life; HDRS: Hamilton Depression Rating Scale; HARS: Hamilton Anxiety Rating Scale.
^a Continuous variables are expressed as mean±SD. Categorical variables are expressed as frequency (percent).

Regarding family history, 14 patients (14.43%) reported a family history of constipation or related disorders. Among these, 10 were male (23.26%), and 4 were female (7.41%),

with this difference reaching statistical significance ($p=0.047$), indicating that males were more likely to report a family history (Fig. 2C). Educational levels is illustrated in Fig. 2D.

In terms of Hoehn-Yahr staging, the distribution of patients is shown in Fig.2E. Overall, there was no significant difference in the distribution of Hoehn-Yahr stages between genders ($p=0.821$)

In the assessment of NMSS, the overall score was 72.25 (SD=66.41), with male patients scoring an average of 71.42 (SD=68.45) and female patients 72.91 (SD=65.38), showing no significant gender differences ($p=0.821$) (Fig. 2F). Specific scores were as follows: cardiovascular function (4.54±5.83), sleep/fatigue (12.67±10.60), mood/apathy (16.18±17.01), perceptual problems/hallucinations (4.81±7.24), attention/memory (6.46±8.36), gastrointestinal function (6.79±6.98), urinary function (7.12±7.84), sexual function (4.47±6.99), and other symptoms (9.20±10.05). These scores did not differ significantly by gender.

In the evaluation of COPA-AUT, the overall score was 16.27 (SD=10.79), with male patients scoring 16.65 (SD=10.91) and female patients 15.96 (SD=10.79), showing no significant difference in scores between genders ($p=0.788$) (Fig. 2G). Detailed scoring included gastrointestinal function (4.55±3.47), urinary function (4.65±3.58), cardiovascular function (2.06±1.99), thermoregulatory function (2.66±2.36), pupillary movement (0.64±0.77), and sexual function (1.71±2.48). There were no significant differences between genders in these scores, except for sexual function, where male patients scored higher ($p=0.023$).

The average Wexner constipation score was 9.45 (SD=4.89), with male patients scoring 9.33 (SD=5.20) and female patients 9.56 (SD=4.68), with no significant difference observed ($p=0.820$) (Fig. 2H). The PAC-QOL overall score was 57.98 (SD=20.52), with males scoring 55.74 (SD=20.52) and females 59.76 (SD=20.55), also showing no significant gender differences ($p=0.279$) (Fig. 2I). The HDRS averaged 15.15 (SD=11.62), with male patients at 14.72 (SD=12.05) and female patients at 15.50 (SD=11.36), again with no significant differences ($p=0.603$) (Fig. 2J). The HARS had an average score of 13.79 (SD=10.63), with males scoring 14.00 (SD=12.29) and females 13.63 (SD=9.23), with no significant differences ($p=0.708$) (Fig. 2K).

Among the 97 patients, 52 (53.6%) reported using laxatives or suppositories within the past month, with 18 patients (18.6%) reporting occasional use (1-2 times per week), 24 patients (24.7%) reporting frequent use (≥ 3 times per week), and 10 patients (10.3%) using laxatives or suppositories almost daily. No significant differences in laxative or suppository usage frequency were observed between genders ($p>0.05$).

In the analysis of younger ($n=28$) and older ($n=69$) patients, a significant difference in literacy rates was observed; illiteracy was lower among younger patients (7.14%) compared to older patients (24.64%) ($p=0.002$) (Fig. 2L). Regarding Hoehn-Yahr staging, a higher proportion of younger patients were at Stage 1.0 (39.29%), while a higher proportion of older patients were at Stage 3.0 (33.33%), with this difference being statistically significant ($p=0.002$) (Fig. 2M). Other scores (NMSS, SCOPA-AUT, Wexner constipation score, PAC-QOL, HDRS, HARS) showed no significant differences between age groups.

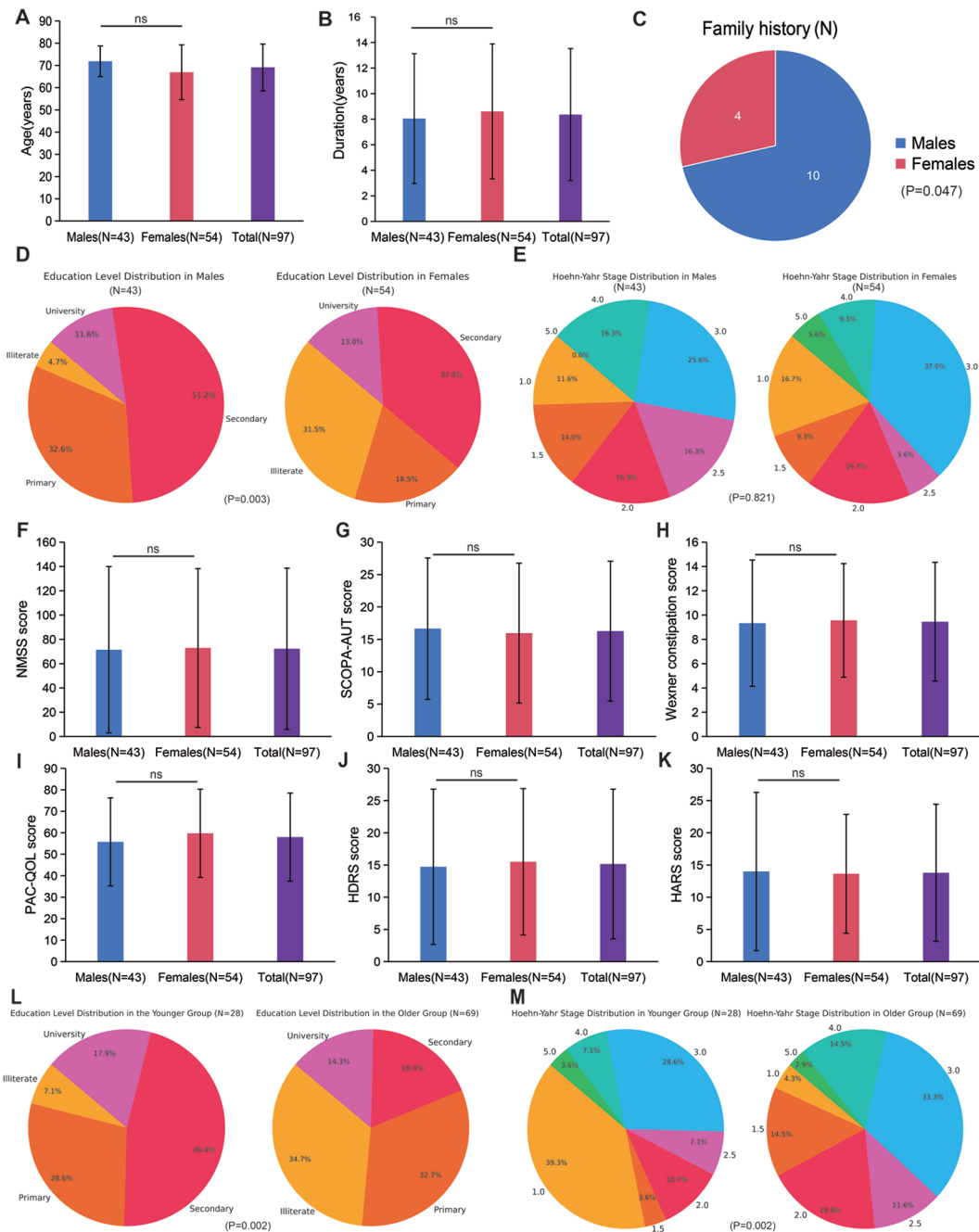


Fig. 2. Characteristics and data interpretation of 97 patients. Note: (A) Average age of patients. (B) Average disease duration of patients. (C) Family history of constipation or related diseases in patients. (D) Education level of patients. (E) Distribution of Hoehn-Yahr stages in patients. (F) NMSS assessment in patients. (G) SCOPA-AUT assessment in patients. (H) Wexner constipation scores of patients. (I) PAC-QOL in patients. (J) HDRS in patients. (K) HARS in patients. (L) Education levels of younger and older patients. (M) Hoehn-Yahr stages of younger and older patients.

These data suggest that while gender and age may influence the educational levels and Hoehn-Yahr staging of PD patients, they do not significantly impact the severity of constipation or the assessment of non-motor symptoms. These findings can guide clinicians in evaluating and managing PD patients, considering gender and age differences to provide more personalized treatment plans.

Significant Correlation Between Constipation Severity, Non-Motor Symptoms, and Quality of Life

This study thoroughly explored the correlation between the severity of constipation and various non-motor symptoms in PD

patients (Table IV, Fig. 3). The Wexner constipation score showed a significant moderate correlation with the NMSS, the SCOPA-AUT, the PAC-QOL, the HDRS, and the HARS. Specifically, the Wexner constipation score positively correlated with the total NMSS and sub-scores (Fig. 3A). The correlation coefficients for cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function, and other symptoms were 0.315, 0.195, 0.125, 0.320, 0.284, 0.404, 0.359, 0.373, and 0.258, respectively, with *p*-values all less than 0.001. These findings indicate a significant association between the severity of constipation and these non-motor symptoms.

Table IV. Association between Wexner constipation score and other core symptoms in constipation patients with PD

	Wexner constipation score			
	Coefficient ^a	p	Coefficient ^a	p ^b
NMSS score				
Cardiovascular	0.315	<0.001	0.195	0.024
Sleep/Fatigue	0.195	<0.001	0.122	0.012
Mood/Apathy	0.125	<0.001	0.096	0.001
Perceptual problems/ Hallucinations	0.320	<0.001	0.256	<0.001
Attention/Memory	0.284	<0.001	0.211	<0.001
Gastrointestinal	0.404	<0.001	0.357	<0.001
Urinary	0.359	<0.001	0.275	<0.001
Sexual function	0.373	<0.001	0.318	<0.001
Others	0.258	<0.001	0.191	<0.001
Total scores	0.038	<0.001	0.034	<0.001
SCOPA-AUT score				
Gastrointestinal	0.959	<0.001	0.822	<0.001
Urinary	0.615	<0.001	0.552	<0.001
Cardiovascular	0.813	0.001	0.599	0.018
Thermoregulatory	0.689	0.001	0.597	0.004
Pupillomotor	1.913	0.003	1.817	0.007
Sexual function	0.750	<0.001	0.910	<0.001
Total scores	0.267	<0.001	0.249	<0.001
PAC-QOL score	0.175	<0.001	0.165	<0.001
HDRS score	0.208	<0.001	0.198	<0.001
HARS score	0.240	<0.001	0.213	<0.001

For abbreviations see Table III. ^a β coefficient. ^b Adjusted for gender, sex, disease duration, family of history, education levels and Hoehn-Yahr staging.

In the multivariable regression analysis, we adjusted for age, gender, disease duration, family history, and education level. The adjusted correlations remained significant. After adjustment, the correlations between constipation scores and the sub-scores for cardiovascular, sleep/fatigue, mood/

apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function, and other symptoms were 0.195, 0.122, 0.096, 0.256, 0.211, 0.357, 0.275, 0.318, and 0.191, respectively, with *p*-values all less than 0.001. This further supports the stable and significant association between the severity of constipation and non-motor symptoms.

Regarding SCOPA-AUT scores (Figure 3B), the Wexner constipation score showed significant positive correlations with the SCOPA-AUT total score and its sub-scores, particularly in gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillary movement, and sexual function aspects. Specifically, the correlation coefficients between constipation scores and these sub-scores were 0.959, 0.615, 0.813, 0.689, 1.913, and 0.750, respectively, with *p*-values all less than 0.001. After adjustment, the correlation coefficients were 0.822, 0.552, 0.599, 0.597, 1.817, and 0.910, respectively, with significant *p*-values. This indicates that the severity of constipation significantly impacts various aspects of autonomic function.

Additionally, the Wexner constipation score was closely associated with the PAC-QOL score, with a correlation coefficient of 0.175, adjusted to 0.165, with *p*-values less than 0.001 (Fig. 3C). This indicates that constipation significantly impacts patients' quality of life. The Wexner constipation score also showed significant correlations with HDRS and HARS scores, with coefficients of 0.208 and 0.240, adjusted to 0.198 and 0.213, all with *p*-values less than 0.001 (Figs. 3D, E). These results suggest a significant association between the severity of constipation and symptoms of depression and anxiety.

Gender Differences in the Association Between Wexner Constipation Scores and Other Non-Motor Symptoms

In this study, we analyzed the relationship between Wexner constipation scores and other core symptoms in PD patients, conducting a detailed comparative analysis between male and female patients. The results showed significant correlations between Wexner constipation scores and non-motor symptom scales (Table V, Fig. 4).

In male patients (Figures 4A-E), the Wexner constipation score did not show statistically significant correlations with NMSS

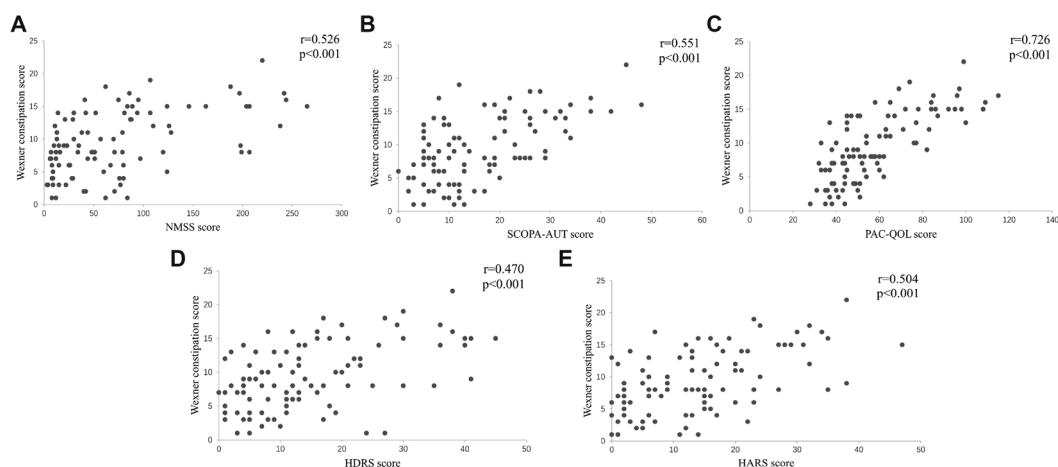


Fig. 3. Correlation between Wexner constipation scores and NMSS scores in 97 patients. Note: (A) Correlation between Wexner constipation scores and NMSS scores. (B) Correlation between Wexner constipation scores and SCOPA-AUT scores. (C) Correlation between Wexner constipation scores and PAC-QOL scores. (D) Correlation between Wexner constipation scores and HDRS scores. (E) Correlation between Wexner constipation scores and HARS scores.

Table V. Association between Wexner constipation score and other core symptoms in male and female patients

	Wexner constipation score							
	Male				Female			
	Coefficient ^a	p	Coefficient ^a	p ^b	Coefficient ^a	p	Coefficient ^a	p ^b
NMSS score								
Cardiovascular	0.256	0.049	0.101	0.506	0.288	0.010	0.278	0.015
Sleep/Fatigue	0.163	0.020	0.074	0.380	0.157	0.012	0.142	0.025
Mood/Apathy	0.110	0.020	0.075	0.167	0.118	0.001	0.114	0.002
Perceptual problems/ Hallucinations	0.354	0.003	0.278	0.033	0.240	0.003	0.241	0.002
Attention/Memory	0.282	0.033	0.226	0.024	0.226	0.002	0.208	0.004
Gastrointestinal	0.332	0.001	0.331	0.014	0.423	<0.001	0.406	<0.001
Urinary	0.302	0.001	0.227	0.014	0.343	<0.001	0.303	<0.001
Sexual function	0.359	<0.001	0.291	0.010	0.321	0.001	0.349	0.001
Others	0.233	0.001	0.210	0.005	0.213	0.001	0.195	0.003
Total scores	0.039	<0.001	0.032	0.014	0.038	<0.001	0.036	<0.001
SCOPA-AUT score								
Gastrointestinal	0.891	<0.001	1.042	<0.001	0.834	<0.001	0.797	<0.001
Urinary	0.869	<0.001	0.776	0.001	0.474	0.004	0.424	0.015
Cardiovascular	0.891	0.018	0.645	0.135	0.737	0.027	0.575	0.087
Thermoregulatory	0.762	0.035	0.665	0.090	0.643	0.011	0.621	0.013
Pupillomotor	2.005	0.054	2.110	0.056	1.859	0.026	1.790	0.038
Sexual function	1.106	<0.001	0.987	<0.001	0.337	0.297	0.731	0.042
Total scores	0.333	<0.001	0.345	<0.001	0.214	<0.001	0.199	0.001
PAC-QOL score	0.184	<0.001	0.171	<0.001	0.170	<0.001	0.165	<0.001
HDRS score	0.207	0.001	0.182	0.008	0.210	<0.001	0.213	<0.001
HARS score	0.250	<0.001	0.228	0.001	0.227	0.001	0.201	0.004

For abbreviations see Table III. ^a β coefficient. ^b Adjusted for age, disease duration, family of history, education levels and Hoehn–Yahr staging.

sub-scores for cardiovascular function (adj. $\rho=0.101$, $p=0.506$), sleep/fatigue (adj. $\rho=0.074$, $p=0.380$), or mood/apathy (adj. $\rho=0.075$, $p=0.167$). However, significant correlations were found with perceptual problems/hallucinations (adj. $\rho=0.278$, $p=0.033$), attention/memory (adj. $\rho=0.226$, $p=0.024$), gastrointestinal function (adj. $\rho=0.331$, $p=0.014$), urinary function (adj. $\rho=0.227$, $p=0.014$), and sexual function (adj. $\rho=0.291$, $p=0.010$). Additionally, there was a significant correlation between Wexner constipation scores and the total NMSS score (adj. $\rho=0.032$, $p=0.014$).

For the SCOPA-AUT scores, significant correlations were observed between Wexner constipation scores and gastrointestinal (adj. $\rho=1.042$, $p<0.001$), urinary (adj. $\rho=0.776$, $p=0.001$), and sexual function (adj. $\rho=0.987$, $p<0.001$). Moreover, Wexner constipation scores were significantly correlated with PAC-QOL (adj. $\rho=0.171$, $p<0.001$), HDRS (adj. $\rho=0.182$, $p=0.008$), and HARS (adj. $\rho=0.228$, $p=0.001$) scores.

In female patients (Figures 4F–J), the Wexner constipation score showed significant correlations with NMSS sub-scores for cardiovascular function (adj. $\rho=0.278$, $p=0.015$), sleep/fatigue (adj. $\rho=0.142$, $p=0.025$), mood/apathy (adj. $\rho=0.114$, $p=0.002$), perceptual problems/hallucinations (adj. $\rho=0.241$, $p=0.002$), attention/memory (adj. $\rho=0.208$, $p=0.004$), gastrointestinal function (adj. $\rho=0.406$, $p<0.001$), urinary function (adj. $\rho=0.303$, $p<0.001$), and sexual function (adj. $\rho=0.349$, $p=0.001$). The Wexner constipation score was also significantly correlated with the total NMSS score (adj. $\rho=0.036$, $p<0.001$).

For SCOPA-AUT scores, significant correlations were found between Wexner constipation scores and gastrointestinal (adj. $\rho=0.797$, $p<0.001$), urinary (adj. $\rho=0.424$, $p=0.015$), cardiovascular (adj. $\rho=0.575$, $p=0.087$), thermoregulatory (adj. $\rho=0.621$, $p=0.013$), pupillary movement (adj. $\rho=1.790$, $p=0.038$), and sexual function (adj. $\rho=0.731$, $p=0.042$). Additionally, significant correlations were observed between Wexner constipation scores and PAC-QOL (adj. $\rho=0.165$, $p<0.001$), HDRS (adj. $\rho=0.213$, $p<0.001$), and HARS (adj. $\rho=0.201$, $p=0.004$) scores.

In summary, significant correlations were observed between Wexner constipation scores and various non-motor symptom scales in both male and female patients. This indicates that the severity of constipation not only affects the quality of life in PD patients but is also closely related to multiple non-motor symptoms, with these associations being particularly pronounced in female patients. These findings highlight the importance of comprehensive assessment and management of constipation and non-motor symptoms in clinical practice for PD patients.

Differences in the Impact of Constipation Severity Among Different Age Groups in PD Patients

This study reveals significant associations between constipation severity and non-motor symptoms, autonomic symptoms, quality of life, anxiety, and depression in both young

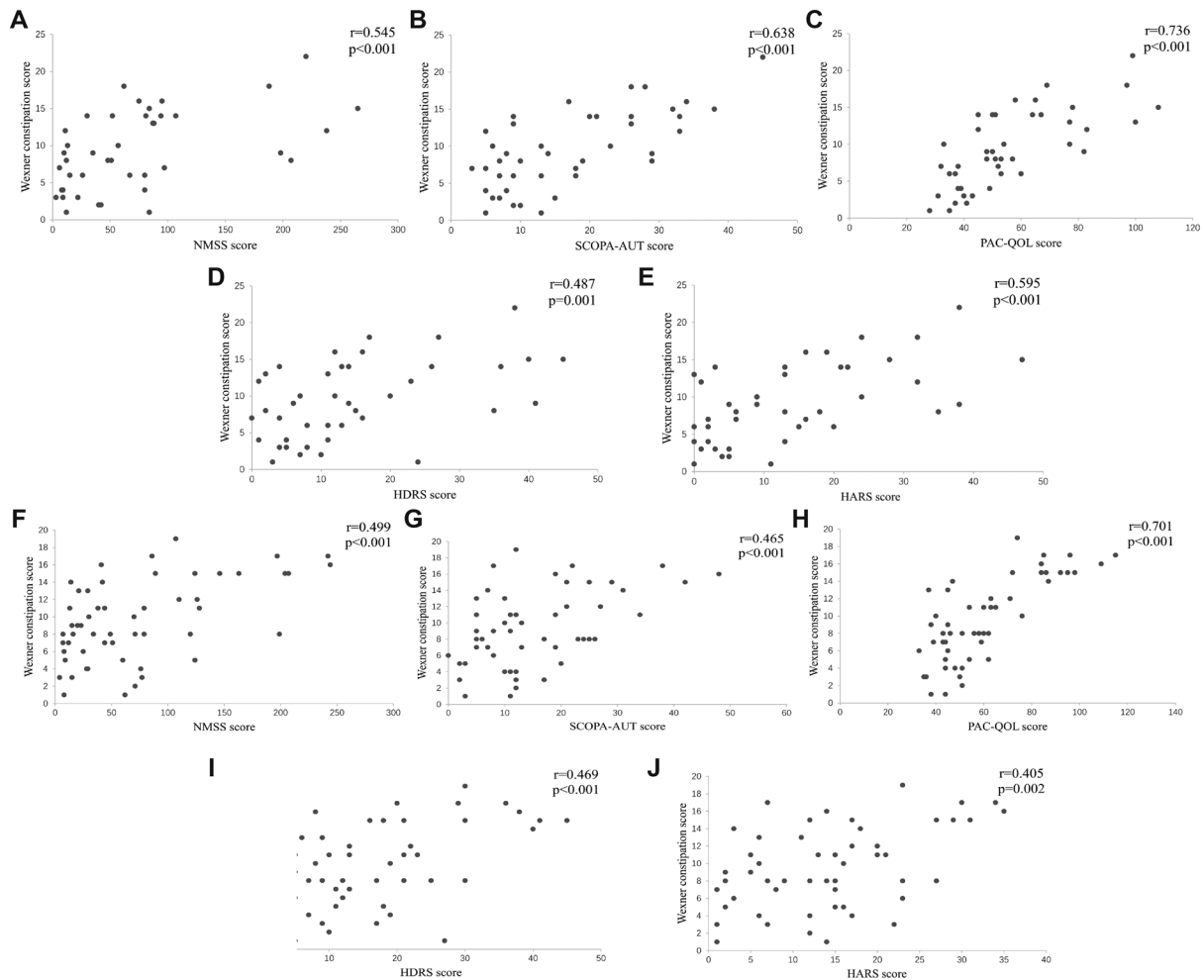


Fig. 4. Correlation between Wexner constipation scores and NMSS, SCOPA-AUT, PAC-QOL, HDRS, and HARS scores in male and female patients. Note: (A) Wexner constipation and NMSS scores in male patients are correlated. (B) Correlation between Wexner constipation scores and SCOPA-AUT scores in male patients. (C) Correlation between Wexner constipation scores and PAC-QOL scores in male patients. (D) Correlation between Wexner constipation scores and HDRS scores in male patients. (E) Correlation between Wexner constipation scores and HARS scores in male patients. (F) Correlation between Wexner constipation scores and NMSS scores in female patients. (G) Correlation between Wexner constipation scores and SCOPA-AUT scores in female patients. (H) Correlation between Wexner constipation scores and PAC-QOL scores in female patients. (I) Correlation between Wexner constipation scores and HDRS scores in female patients. (J) Correlation between Wexner constipation scores and HARS scores in female patients.

and older PD patients through subgroup analysis (Table VI, Fig. 5). In the younger patient group (Figs. 5A-E), the severity of constipation showed no significant correlation with several NMSS sub-scores, including cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal, and urinary symptoms. However, there were significant correlations between constipation severity and sexual function, other symptoms, and the total NMSS score. Additionally, in the SCOPA-AUT scores, significant correlations were found with gastrointestinal function, sexual function, and the total score but not cardiovascular function and thermoregulation.

In the older patient group (Figures 5F-J), the severity of constipation showed significant positive correlations with several NMSS sub-scores, including cardiovascular function, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal, and urinary symptoms. Significant correlations were found

between constipation severity and multiple SCOPA-AUT sub-scores, including gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillary movement, sexual function, and the total score. Notably, constipation severity was also positively correlated with PAC-QOL, HDRS, and HARS scores in the older group, indicating a substantial impact on quality of life, depression, and anxiety symptoms.

Multivariable regression analysis, adjusting for gender, disease duration, family history, education level, and Hoehn-Yahr stage, revealed that only the PAC-QOL scale showed statistically significant correlations in the younger group. In contrast, most non-motor symptom scales in the older group showed significant correlations. This indicates that constipation affects PD patients differently across age groups, with a more pronounced impact on non-motor symptoms and quality of life in older patients. These findings provide crucial insights for the comprehensive assessment and management of constipation and related non-motor symptoms in clinical practice for PD patients.

Table VI. Association between Wexner constipation score and other core symptoms in younger and older patients

	Wexner constipation score							
	Younger patients				Older patients			
	Coefficient ^a	p	Coefficient ^a	p ^b	Coefficient ^a	p	Coefficient ^a	p ^b
NMSS score								
Cardiovascular	0.254	0.120	0.245	0.170	0.264	0.007	0.103	0.277
Sleep/Fatigue	0.061	0.445	0.058	0.525	0.192	0.001	0.112	0.007
Mood/Apathy	0.022	0.641	0.020	0.733	0.155	<0.001	0.112	0.003
Perceptual problems/ Hallucinations	0.119	0.288	0.141	0.259	0.351	<0.001	0.259	0.002
Attention/Memory	0.039	0.736	0.068	0.641	0.304	<0.001	0.234	0.001
Gastrointestinal	0.353	0.024	0.402	0.038	0.374	<0.001	0.305	0.001
Urinary	0.571	<0.001	0.631	0.001	0.276	<0.001	0.209	0.002
Sexual function	0.196	0.202	0.251	0.148	0.356	<0.001	0.299	<0.001
Others	0.202	0.018	0.216	0.028	0.226	<0.001	0.173	0.002
Total scores	0.020	0.129	0.022	0.157	0.044	<0.001	0.035	<0.001
SCOPA-AUT score								
Gastrointestinal	0.584	0.015	0.601	0.032	0.957	<0.001	0.900	<0.001
Urinary	0.512	0.072	0.525	0.117	0.632	<0.001	0.512	0.001
Cardiovascular	0.725	0.141	0.706	0.207	0.785	0.007	0.427	0.151
Thermoregulatory	0.582	0.077	0.563	0.123	0.784	0.003	0.528	0.039
Pupillomotor	1.359	0.212	1.254	0.325	2.368	0.003	1.505	0.066
Sexual function	0.626	0.039	0.800	0.020	0.851	0.001	0.840	0.001
Total scores	0.233	0.004	0.231	0.011	0.276	<0.001	0.240	<0.001
PAC-QOL score	0.173	<0.001	0.175	<0.001	0.173	<0.001	0.153	<0.001
HDRS score	0.124	0.076	0.123	0.133	0.247	<0.001	0.205	<0.001
HARS score	0.164	0.031	0.169	0.055	0.268	<0.001	0.218	<0.001

For abbreviations see Table III. ^a β coefficient. ^b Adjusted for gender, disease duration, family of history, education levels and Hoehn-Yahr staging.

MR Analysis Results Reveal No Significant Causal Relationships Between Constipation, Mental Health, and Sleep Disorders

In this study, we employed multiple MR methods to assess the causal relationships between constipation severity and anxiety, depression, and sleep disorders (Fig. 6). Specifically, we used five methods: IVW, MR-Egger regression, WME, simple mode, and weighted mode.

The MR analysis to determine the causal relationship between constipation severity and anxiety (Table VII, Figs 6A, B) employed five different methods: IVW, MR-Egger regression, WME, simple mode, and weighted mode. All five MR analysis methods failed to demonstrate a significant causal relationship between the severity of constipation and anxiety. The IVW analysis showed an effect size (b) of 0.0407, a standard error (SE) of 0.0456, and a *p*-value of 0.3715; the estimated odds ratio (OR) was 1.0416, with a 95% confidence interval (CI) ranging from 0.9525 to 1.1391. The MR-Egger regression yielded an effect size (b) of -0.0326 with a SE of 0.3021 and a *p*-value of 0.9144 (estimated OR=0.9679, 95%CI: 0.5354-1.7497). The WME method produced an effect size of 0.0373 with a SE of 0.0638 and a *p*-value of 0.5587 (estimated OR=1.0380, 95%CI: 0.9160- 1.1763). The simple mode analysis reported an effect size of 0.0551 with a SE of 0.1463 and a

p-value of 0.7080, (estimated OR was 1.0567 with a 95%CI: 0.7933-1.4075). The weighted mode method showed an effect size of 0.0585, a SE of 0.1373, and a *p*-value of 0.6719 (estimated OR=1.0603, 95%CI: 0.8101 to 1.3878).

The MR analysis to evaluate the causal relationship between constipation severity and depression (Table VIII, Figs. 6C, D) used five methods: IVW, MR-Egger regression, WME, simple mode, and weighted mode. All five MR analysis methods failed to demonstrate a significant causal relationship between the severity of constipation and depression. The IVW analysis showed an effect size of -0.0103, a SE of 0.1107, and a *p*-value of 0.9259 (estimated OR=0.9898, 95%CI: 0.7967-1.2296). The MR-Egger regression yielded an effect size of 0.2027, a SE of 0.7403, and a *p*-value of 0.7855, (estimated OR=1.2247, 95%CI: 0.2870-5.2257). The WME method produced an effect size of -0.0080 with a SE of 0.1385 and a *p*-value of 0.9540 (estimated OR=0.9920, 95%CI: 0.7561-1.3015). The simple mode analysis reported an effect size of 0.0010 with a SE of 0.3388 and a *p*-value of 0.9977 (OR=1.0010, 95%CI: 0.5152-1.9447). The weighted mode method showed an effect size of -0.0084, a SE of 0.3394, and a *p*-value of 0.9803 (estimated OR=0.9916, 95%CI: 0.5098-1.9286).

The MR analysis used various methods to evaluate the causal relationship between constipation severity and sleep

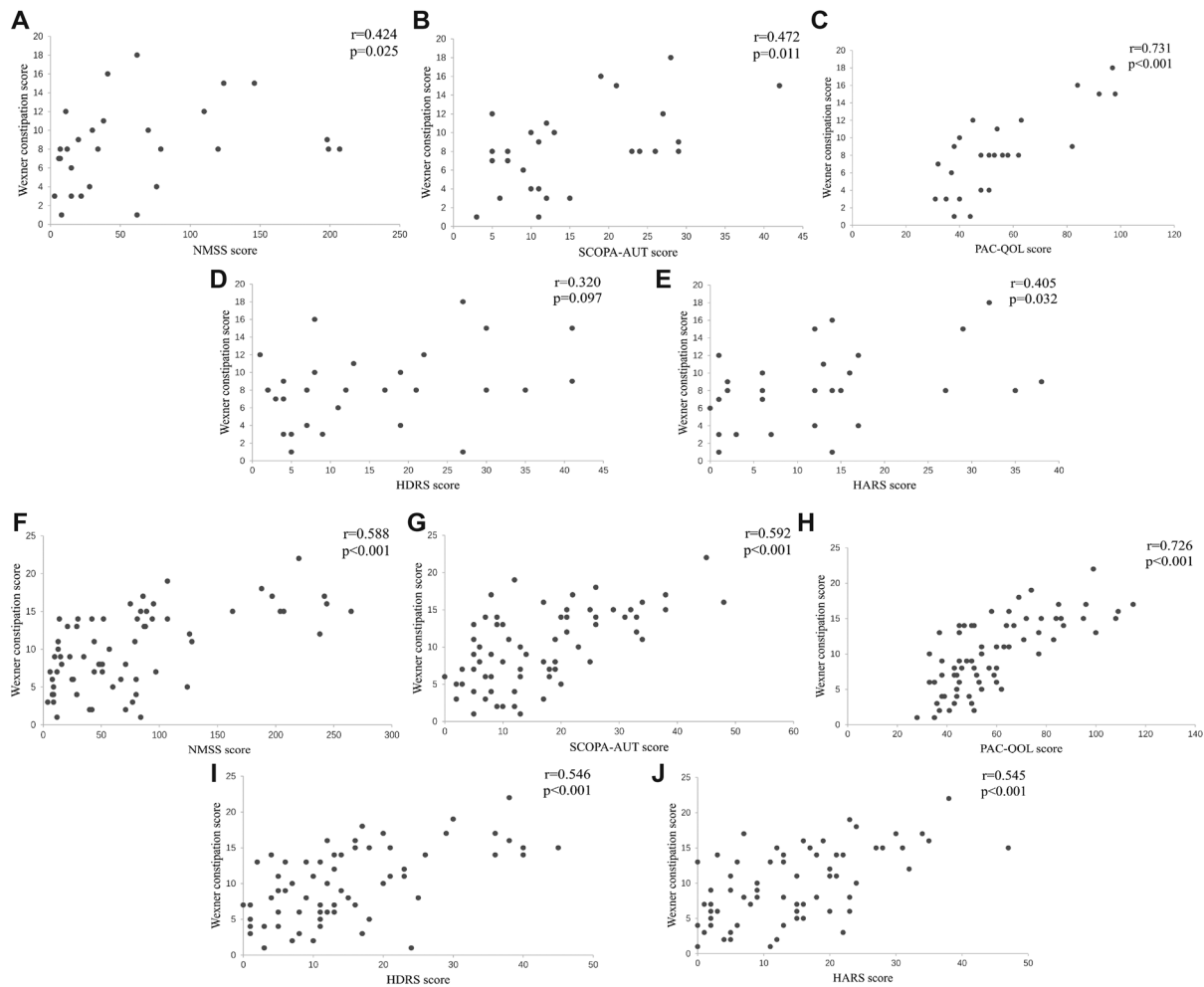


Fig. 5. Correlation between Wexner constipation scores and NMSS, SCOPA-AUT, PAC-QOL, HDRS, and HARS scores in young and older patients. Note: (A) Correlation between Wexner constipation and NMSS scores in young patients. (B) Correlation between Wexner constipation scores and SCOPA-AUT scores in young patients. (C) Correlation between Wexner constipation scores and PAC-QOL scores in young patients. (D) Correlation between Wexner constipation scores and HDRS scores in young patients. (E) Correlation between Wexner constipation scores and HARS scores in young patients. (F) Correlation between Wexner constipation scores and NMSS scores in older patients. (G) Correlation between Wexner constipation scores and SCOPA-AUT scores in older patients. (H) Correlation between Wexner constipation scores and PAC-QOL scores in older patients. (I) Correlation between Wexner constipation scores and HDRS scores in older patients. (J) Correlation between Wexner constipation scores and HARS scores in older patients.

disorders (Table IX, Figs. 6E, F). All methods did not show significant causal relationship. The IVW method showed an effect size (OR) of 0.997 with a 95%CI: 0.911-1.090 and a p -value of 0.944. The MR-Egger method yielded an effect size of 0.755 with a 95%CI: 0.419-1.360 and a p -value of 0.355. The WME method produced an effect size of 0.947 with a 95%CI: 0.838-1.070 and a p -value of 0.382. The simple mode method showed an effect size of 0.918 with a 95%CI: 0.670-1.256 and a p -value of 0.595, and the weighted mode method showed an effect size of 0.914 with a 95%CI: 0.694-1.204 and a p -value of 0.526.

In summary, this study used multiple MR methods to evaluate the causal relationships between constipation severity and anxiety, depression, and sleep disorders. The results showed no significant causal relationships for anxiety, depression, or sleep disorders. These findings provide essential genetic epidemiological evidence for further research on the relationship between constipation and mental health and sleep

disorders, suggesting the need for more studies to explore the potential mechanisms of how constipation affects mental health.

Causal Relationship Analysis Between Constipation, Anxiety, Depression, and Sleep Disorders

In this study, we examined the causal relationships between the severity of constipation and anxiety and depression using the IVW method and MR-Egger regression to test for heterogeneity (Fig. 7).

For the relationship between constipation and anxiety, the IVW method yielded a Q-statistic of 108.16 with 111 degrees of freedom ($p=0.5585$), while the MR-Egger method produced a Q-statistic of 107.04 with 110 degrees of freedom ($p=0.5622$). Both methods showed no significant heterogeneity, indicating no substantial differences among the selected SNPs and suggesting that the causal estimates are stable and not influenced by individual SNPs (Fig. 7A). This consistency

Table VII. Results of MR analysis of the association between constipation and anxiety

MR Analysis Method	SNP Quantity	β	SE	OR (95% CI)	p-value
MR Egger	47	0.040773324	0.045627044	0.952509039	0.371524246
Weighted median	47	-0.03264652	0.302077983	0.535411662	0.914418106
Inverse variance weighted	47	0.037316784	0.063821883	0.915967765	0.55874809
Simple mode	47	0.055124415	0.146268974	0.793292897	0.70800307
Weighted mode	47	0.058545161	0.137343555	0.81005899	0.671900759

MR: Mendelian randomization; SNP: single nucleotide polymorphism; β : effect size; SE: standard error; OR: odds ratio; CI: confidence interval.

indicates that the potential causal impact of constipation severity on anxiety is uniform across different study samples, enhancing the reliability of the study's conclusions. Although specific effect sizes and *p*-values varied between methods,

the overall trend was consistent, indicating a stable causal relationship between constipation severity and anxiety.

For the relationship between constipation and depression, the IVW method yielded a Q-statistic of 108.16 with 111

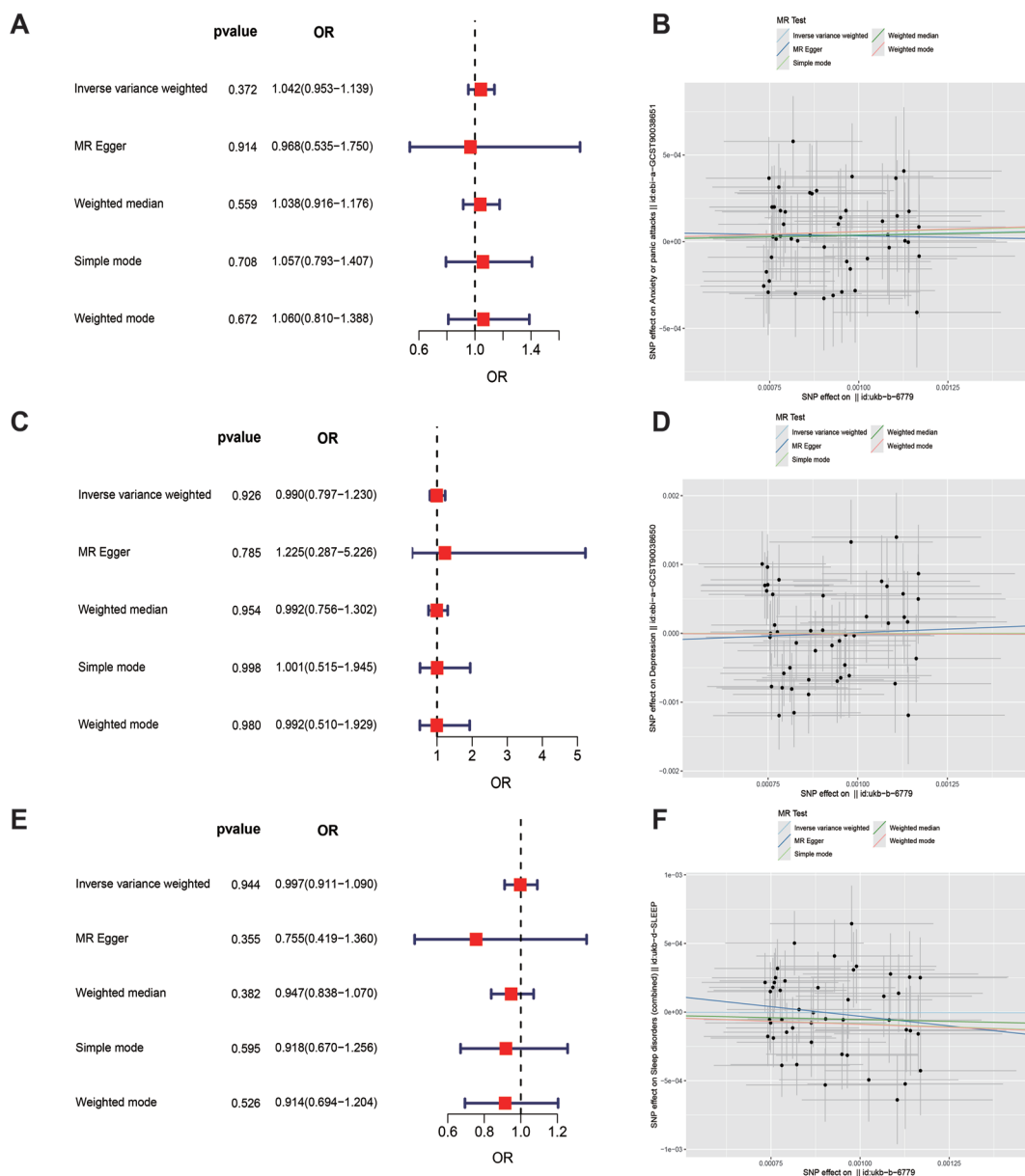


Fig. 6. MR analysis results for constipation and its relationships with anxiety, depression, and sleep disorders. Note: (A) Forest plot of MR analysis results for constipation and anxiety. (B) Scatter plot of the relationship between constipation and anxiety. (C) Forest plot of MR analysis results for constipation and depression. (D) Scatter plot of the relationship between constipation and depression. (E) Forest plot of MR analysis results for constipation and sleep disorders. (F) Scatter plot of the relationship between constipation and sleep disorders.

Table VIII. Results of MR analysis of the association between constipation and depression

MR Analysis Method	SNP Quantity	β	SE	OR (95% CI)	p-value
MR Egger	47	-0.010289651	0.110693316	0.796722732	0.925938204
Weighted median	47	0.20267463	0.740257954	0.287012084	0.785499447
Inverse variance weighted	47	-0.007999703	0.138535956	0.75613891	0.953952072
Simple mode	47	0.000986434	0.338848816	0.515222081	0.997689843
Weighted mode	47	-0.008424769	0.339400384	0.50984449	0.980303908

For abbreviations see Table VII.

Table IX. Results of MR analysis of the association between constipation and sleep disorders

MR Analysis Method	SNP Quantity	β	SE	OR (95% CI)	p-value
MR Egger	46	-0.003232237	0.045639699	0.911479616	0.943540422
Weighted median	46	-0.280826677	0.300317495	0.419182469	0.354841052
Inverse variance weighted	46	-0.054389584	0.062196526	0.838370817	0.381857199
Simple mode	46	-0.08580562	0.160260195	0.670376622	0.594999666
Weighted mode	46	-0.089782293	0.140487319	0.694101248	0.526012327

For abbreviations see Table VII.

degrees of freedom ($p=0.5585$), while the MR-Egger method produced a Q-statistic of 107.04 with 110 degrees of freedom ($p=0.5622$) (Fig. 7B). Both methods showed no significant heterogeneity, indicating that the selected SNPs did not exhibit substantial heterogeneity. This suggests that the causal estimates are stable and not influenced by individual SNPs, reinforcing the reliability of the conclusion that constipation severity has a consistent potential causal effect on depression across different study samples.

For the relationship between constipation and sleep disorders, the IVW method yielded a Q-statistic of 108.16 with 111 degrees of freedom ($p=0.5585$), while the MR-Egger method produced a Q-statistic of 107.04 with 110 degrees of

freedom ($p=0.5622$) (Fig. 7C). Again, both methods showed no significant heterogeneity, indicating that the selected SNPs did not exhibit substantial heterogeneity. This consistency suggests that the potential causal impact of constipation severity on sleep disorders is uniform across different study samples, enhancing the reliability of the study's conclusions.

This study systematically evaluated the causal relationships between constipation severity and anxiety, depression, and sleep disorders using various MR methods and heterogeneity tests. The results showed no significant causal relationships between constipation and anxiety, depression, or sleep disorders. These findings provide essential genetic epidemiological evidence for further research on the relationship between constipation and

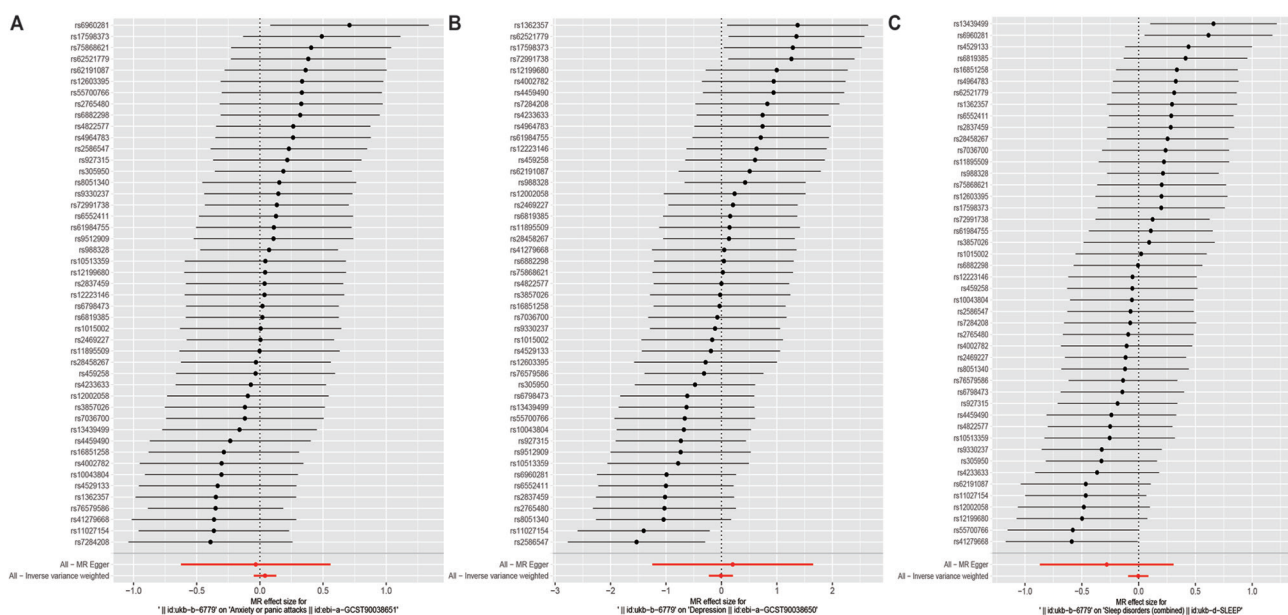


Fig. 7. Forest plots of heterogeneity test results. Note: (A) Forest plot of heterogeneity test results for constipation and anxiety. (B) Forest plot of heterogeneity test results for constipation and depression. (C) Forest plot of heterogeneity test results for constipation and sleep disorders.

mental health and sleep disorders. Additionally, they highlight the need for more studies to explore the potential mechanisms by which constipation affects mental health.

Causal Relationships Between Constipation and Anxiety, Depression, and Sleep Disorders Are Not Significantly Affected by Pleiotropy Bias

In this study, we used funnel plots to assess the potential pleiotropy in the causal relationships between constipation severity and anxiety and depression. Funnel plots, a visual tool for evaluating pleiotropy, plot the effect size of SNPs on the horizontal axis and the inverse of their SE (1/SE) on the vertical axis. This allows us to examine the distribution patterns of individual SNP effect estimates (Fig. 8).

The funnel plot exhibited a generally symmetrical point distribution for the relationship between constipation and anxiety, with most points clustering near the $\beta=0$ center line and no significant bias to either side (Fig. 8A). This symmetry indicates that the selected SNPs as instrumental variables in this study were not significantly affected by pleiotropy bias when assessing the causal effect of constipation severity on anxiety. Although a few points slightly deviated from the center line, suggesting possible heterogeneity or pleiotropy, these deviations were not significant enough to affect the overall robustness of the MR analysis results. Therefore, we can confidently assert that pleiotropy does not influence the causal effect estimates between constipation severity and anxiety.

Similarly, for the potential causal relationship between constipation severity and depression, the funnel plot showed a symmetrical point distribution with most points clustered near the $\beta=0$ center line, indicating no significant bias (Fig. 8B). This suggests that the selected SNPs as instrumental variables were not significantly impacted by pleiotropy bias in revealing the causal effect of constipation severity on depression. While some points slightly deviated from the center line, these deviations were not significant enough to affect the overall robustness of the MR analysis results. Consequently, the causal effect estimates between constipation severity and depression are not influenced by pleiotropy.

The funnel plot for the relationship between constipation and sleep disorders displayed a generally symmetrical point distribution, with most points clustering near the $\beta=0$ center line and no significant bias to either side (Fig. 8C). This symmetry indicates that the selected SNPs as instrumental variables in this study were not significantly affected by pleiotropy bias when assessing the causal effect of constipation severity on sleep disorders. Although a few points slightly deviated from the center line, these deviations were not significant enough to affect the overall robustness of the MR analysis results. Therefore, pleiotropy does not influence the causal effect estimates between constipation severity and sleep disorders.

In summary, the SNPs used as instrumental variables in this study were not significantly impacted by pleiotropy bias when revealing the causal effects of constipation severity on anxiety, depression, and sleep disorders. This enhances the reliability of our conclusions, indicating that the causal effect estimates between constipation severity and these non-motor symptoms are robust and credible.

No Significant Single SNP Influence on the Causal Relationships Between Constipation and Anxiety, Depression, and Sleep Disorders

In this study, we employed the leave-one-out sensitivity analysis to meticulously examine the impact of each SNP on the estimated causal relationships between constipation severity and anxiety, depression, and sleep disorders (Fig. 9). This method allows for the exclusion of each SNP one at a time, followed by the recalculation of the combined causal effect of the remaining SNPs to determine if any single SNP disproportionately influences the overall results.

The forest plot for the sensitivity analysis of the relationship between constipation and anxiety demonstrates that the effect estimates of individual SNPs are closely distributed around the center line, with the overall effect consistency represented by the red summary data point (Fig. 9A). No significant deviation of any single SNP effect estimate was observed, indicating that our findings are unlikely to be excessively influenced

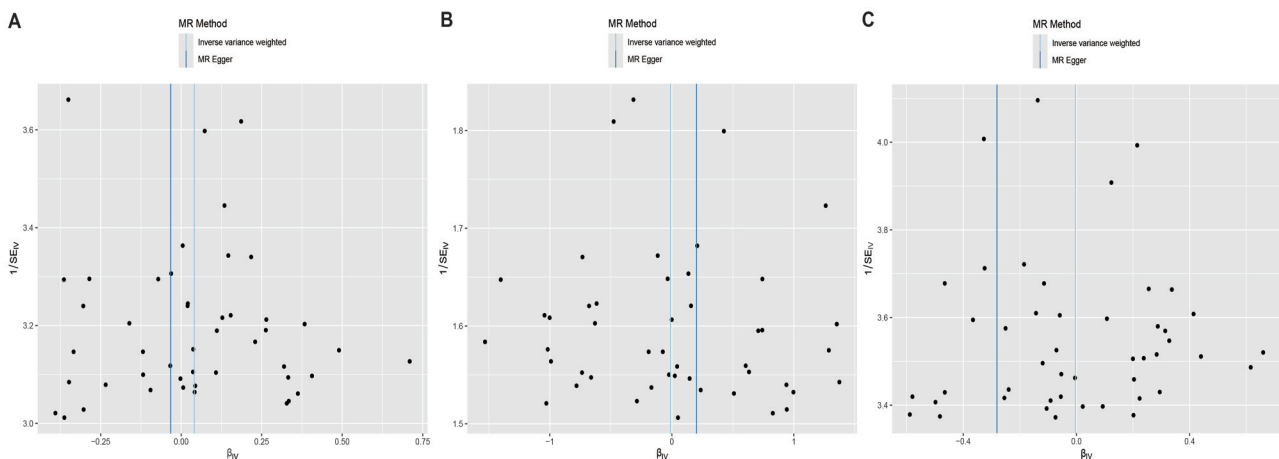


Fig. 8. Funnel plots for pleiotropy test. Note: (A) Funnel plot for pleiotropy test between constipation and anxiety. (B) Funnel plot for pleiotropy test between constipation and depression. (C) Funnel plot for pleiotropy test between constipation and sleep disorders.

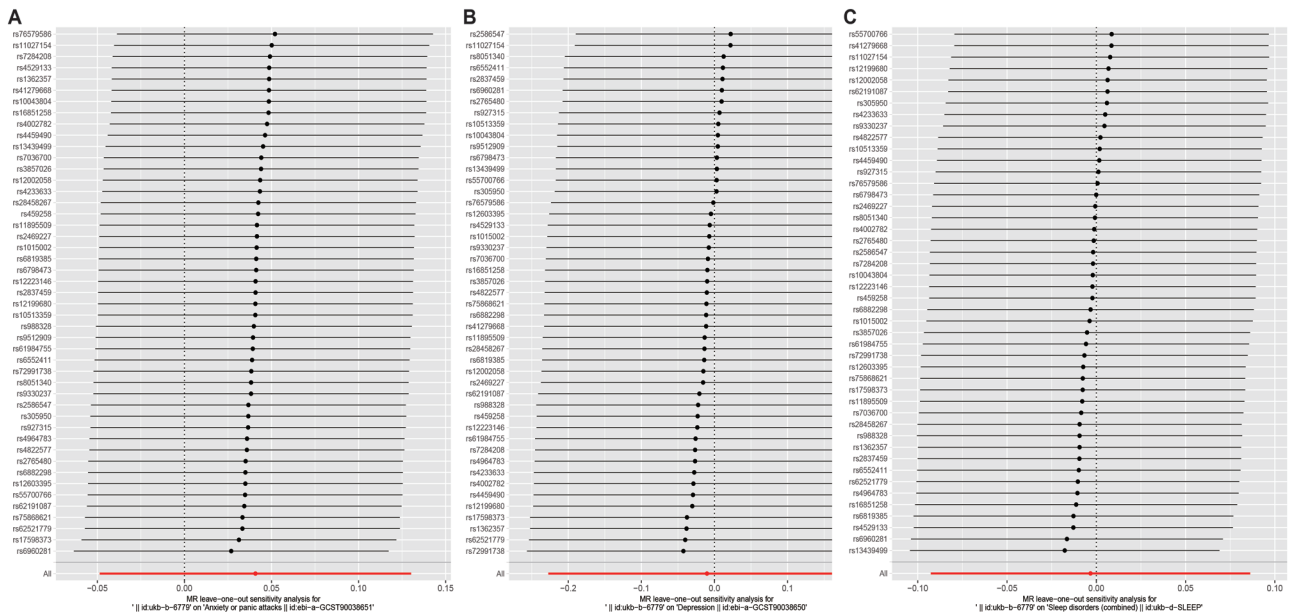


Fig. 9. Forest plots for leave-one-out sensitivity analysis. Note: (A) Forest plot for sensitivity analysis between constipation and anxiety. (B) Forest plot for sensitivity analysis between constipation and depression. (C) Forest plot for sensitivity analysis between constipation and sleep disorders.

by any SNP. This consistency underscores the robustness of the association between constipation severity and anxiety, suggesting that the anomalous effect of any specific SNP does not drive the results. This enhances the reliability of our findings and provides a solid foundation for understanding the complex relationship between constipation and anxiety.

The forest plot for the sensitivity analysis of the relationship between constipation and depression shows that the effect estimates of individual SNPs are closely distributed around the center line, with the overall effect consistency represented by the red summary data point (Fig. 9B). No significant deviation of any single SNP effect estimate was observed, indicating that our findings are unlikely to be disproportionately influenced by any SNP. This consistency underscores the robustness of the association between constipation severity and depression, further enhancing the reliability of our conclusions and providing a solid foundation for understanding the complex relationship between constipation and depression.

Similarly, the forest plot for the sensitivity analysis of the relationship between constipation and sleep disorders demonstrates that the effect estimates of individual SNPs are closely distributed around the center line, with the overall effect consistency represented by the red summary data point (Fig. 9C). No significant deviation of any single SNP effect estimate was observed, indicating that our findings are unlikely to be disproportionately influenced by any SNP. This consistency underscores the robustness of the association between constipation severity and sleep disorders, suggesting that the anomalous effect of any specific SNP does not drive the results. This provides strong evidence for understanding the complex relationship between constipation and sleep disorders.

Based on the results of the leave-one-out sensitivity analysis, we can confidently conclude that the associations between constipation severity and anxiety, depression, and sleep disorders in this study are robust and not driven by the anomalous effects of any specific SNP. This enhances the

reliability of our findings, ensuring that the reported causal relationships are grounded in solid genetic evidence.

DISCUSSION

This study demonstrates that constipation severity is significantly correlated with non-motor symptoms in PD patients, particularly in elderly and female individuals. However, despite observational evidence suggesting a potential link between constipation and mental health disorders such as anxiety and depression [6, 11, 31], our MR analysis did not establish a direct causal relationship [32, 33]. This finding suggests that constipation may be more indicative of underlying autonomic dysfunction in PD rather than being a direct contributor to psychiatric symptoms. Therefore, clinical management should emphasize the comprehensive evaluation and treatment of constipation as part of a holistic approach to improving PD patients' overall well-being.

From a scientific perspective, this study contributes to the growing body of research on the neurological mechanisms underlying non-motor symptoms in PD. Recent studies have highlighted that constipation in PD may be driven by degeneration of dopaminergic neurons in the enteric nervous system and central autonomic dysfunction [34, 35]. Furthermore, dopaminergic and anticholinergic medications commonly used in PD treatment significantly contribute to gastrointestinal dysmotility, exacerbating constipation symptoms [13-15]. By integrating MR analysis, we provide robust genetic evidence that reduces confounding factors and enhances the reliability of causal inferences regarding the role of constipation in PD-related neuropsychiatric symptoms. Clinically, our results underscore the importance of recognizing and managing constipation as a significant component of PD care. The identification of sex- and age-related differences in constipation severity suggests the need for personalized treatment strategies to optimize non-motor

symptom management. Furthermore, our findings highlight the potential benefits of integrating gastrointestinal symptom evaluation into routine PD care to improve patients' quality of life [36, 37].

Despite its strengths, this study has certain limitations. First, the relatively small sample size and single-center design may limit the generalizability of our findings. Future large-scale, multi-center studies are required to confirm these results. Second, while MR analysis provides a powerful approach to infer causality, its accuracy depends on the validity of instrumental variables, and potential pleiotropic effects cannot be completely ruled out. However, our heterogeneity and pleiotropy tests confirmed the robustness of our findings [32, 33]. Additionally, our study did not assess the impact of specific PD medications or their dosages on constipation severity, which remains an important area for future investigation. Longitudinal studies are also needed to explore the dynamic interplay between constipation and non-motor symptoms throughout the progression of PD.

Future research should focus on validating our findings in larger, more diverse PD populations using multi-center cohort studies. Longitudinal studies will be crucial to understanding how constipation influences the progression of non-motor symptoms over time. Further investigation is also needed to identify the most effective treatment strategies for PD-related constipation, including pharmacological interventions, dietary modifications, and gut microbiota-targeted therapies [13, 38]. Advanced neuroimaging and biomarker studies could provide deeper insights into the neural pathways linking constipation to autonomic dysfunction in PD. By integrating genetic, clinical, and neurophysiological approaches, future research can contribute to the development of more personalized and effective management strategies for PD patients (Fig. 10).

CONCLUSIONS

A moderate correlation was found between constipation severity and non-motor symptoms, especially in elderly and female patients with PD. However, no significant causal association was identified between constipation and mental health issues such as anxiety, depression, or sleep disorders.

Conflicts of interest: None to declare.

Authors' contribution: X.Z. and J.J. conceived and designed the study, contributed to the conceptual framework and participated in drafting or critically revising sections of the manuscript. Y.H., Q.W. and J.C. collected data and contributed to initial data analysis and interpretation. Z.Z. conducted the statistical analysis, applied Mendelian randomization techniques, and assisted in writing the methods and results sections. D.G. provided theoretical support for the study and revised the research methodology and discussion, offering expert feedback. J.G. coordinated the overall research process and critically revised the manuscript for important intellectual content. J.S. provided leadership and oversight of the study and ensured the accuracy of the data. All the authors read and approved the final version of the manuscript.

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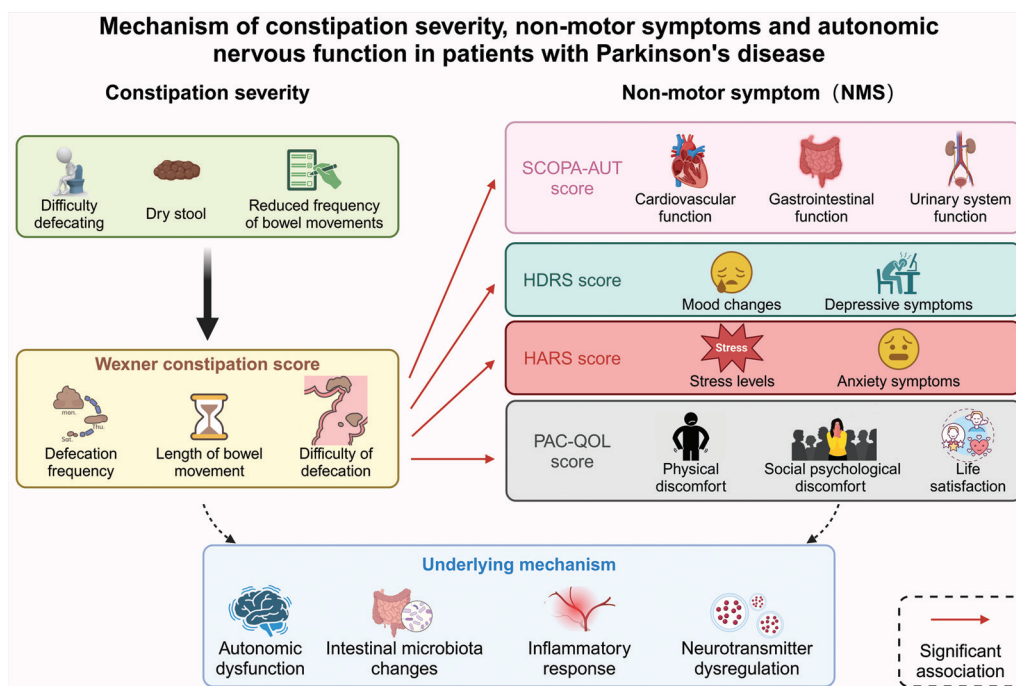


Fig. 10. Mechanism of constipation severity, non-motor symptoms and autonomic nervous function in patients with PD.

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