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Research Article

Therapeutic Effects of a Low FODMAP Diet on Symptoms, Gut Microbiota, and Anxiety in Patients with Irritable Bowel Syndrome

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Background

Individuals with irritable bowel syndrome (IBS) are at an elevated risk for mental disorders. However, IBS management often overlooks psychological factors, which may contribute to suboptimal therapeutic outcomes.

Objective

This study aims to assess the current treatment approach for IBS at our center, Jinling Hospital of Nanjing and investigate whether dietary interventions, specifically the low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet (low FODMAP diet; LFD), could alleviate anxiety symptoms in IBS patients.

Methods

We prospectively enrolled two cohorts of IBS patients. The first cohort underwent an observational study to assess the prevalence of anxiety and evaluate current treatment approaches. The second cohort participated in a clinical trial evaluating the efficacy of the LFD. Stool samples were collected before the LFD intervention and analyzed using 16S rRNA sequencing.

Results

Anxiety was present in approximately 60% of IBS patients in our cohort, but it was frequently overlooked in conventional treatment. Anxiety was positively correlated with IBS symptom severity. Rifaximin was the only standard therapeutic option demonstrating efficacy. A one-month LFD intervention significantly reduced both gastrointestinal and mental health symptoms in IBS patients. Although α- and β-diversity of the gut microbiota were similar between diet responders and non-responders, the composition of dominant bacteria differed significantly. At the genus level, responders exhibited higher abundances of Klebsiella, Parabacteroides, and Lactobacillus than non-responders.

Conclusion

Anxiety is common in IBS patients but often neglected in standard treatment protocols. The LFD may serve as an alternative therapeutic approach, potentially exerting benefits through modulation of gut microbiota.

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1. INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by dysregulated gut–brain interactions. It is classified into four subtypes: IBS with diarrhea (IBS-D), IBS with constipation (IBS-C), IBS with mixed stool patterns (IBS-M), and unclassified IBS (IBS-U), affecting approximately 3.8–9.2% of adults globally.[1,2] Notably, nearly 30% of IBS patients also suffer from mental health disorders, such as anxiety and depression, which exacerbate the severity of IBS symptoms and significantly impair long-term quality of life. Despite this, conventional treatment strategies predominantly focus on alleviating gastrointestinal symptoms, often overlooking the critical role of mental health in disease management.[3]

Anxiety and depression have a profound impact on the course of IBS. Neuromodulators, such as tricyclic antidepressants and selective serotonin reuptake inhibitors, are commonly used to address these mental health disorders by targeting receptors involved in the brain–gut axis. However, these neuromodulators are associated with significant side effects, particularly when used in combination with other medications. These side effects include serotonin syndrome, cardiac complications, and weight gain.[4]

Many IBS patients report that certain foods, such as gluten, wheat, lactose, and milk, may trigger symptom recurrence. Consequently, dietary modification is frequently recommended as a first-line therapeutic strategy, alongside soluble fiber supplementation and antispasmodic drugs.[2,5-7] Specifically, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) are short-chain, poorly absorbed, fermentable sugars that can induce IBS symptoms by increasing visceral hypersensitivity and altering gut microbiota.[8,9]

Emerging evidence supports the efficacy of a low FODMAP diet (LFD) in alleviating gastrointestinal symptoms and enhancing disease-specific quality of life.[10-15] Additionally, preliminary evidence suggests a critical role of the gut microbiota in IBS pathophysiology and management.[16,17] Notably, recent studies suggest that baseline fecal microbiome profiles may help distinguish responders from non-responders to LFD interventions.[18,19]

However, there is limited evidence regarding the impact of LFD on mental health symptoms, particularly anxiety, and the underlying mechanisms remain poorly understood. Therefore, this study has two main objectives: (i) to evaluate the prevalence and clinical correlation of anxiety in a real-world IBS cohort; and (ii) to investigate whether the LFD could alleviate both gastrointestinal and anxiety symptoms in IBS patients and to explore potential gut microbial associations in a pilot interventional study.

2. METHODS

2.1. PARTICIPANTS

For the observational study, patients with a confirmed Rome IV diagnosis of IBS were recruited from outpatient clinics. The eligibility criteria were intentionally broad to capture a real-world population. Baseline data were abstracted from routine clinical records at enrollment.

For the interventional study, participants had a mean symptom duration of over two years. Exclusion criteria for the interventional cohort included severe cardiac, liver, neurological, or psychiatric diseases, as well as gastrointestinal disorders other than IBS (e.g., inflammatory bowel disease, celiac disease) that could explain the current symptoms. Individuals with systemic diseases requiring specialized diets (e.g., cardiovascular disease, chronic renal failure, chronic liver disease, and diabetes mellitus) or those adhering to restrictive diets (e.g., gluten-free or vegan diets) prior to enrollment were also excluded. Common IBS medications were allowed, but probiotics, proton pump inhibitors, antispasmodics, and antibiotics had to be discontinued at least one month prior to inclusion.

The two studies were conducted between January 2022 and December 2022. All participants received detailed verbal and written information about the study and provided written informed consent before participation.

2.2. STUDY PROTOCOL

The study consisted of two components conducted between January 2022 and December 2022: a cross-sectional observational study and a prospective interventional study. For the observational study, patients were enrolled prospectively during the study period. Clinical and questionnaire data were collected at a single time-point upon enrollment to assess the point-prevalence of anxiety and current treatment approaches.

The subsequent prospective, non-randomized clinical study investigated whether the LFD could improve both anxiety and bowel symptoms in IBS patients. Through separate recruitment, eligible patients referred to a senior gastroenterologist were offered the LFD intervention according to the study protocol. The decision to participate in the intervention was based on patient choice.

Outcomes were assessed at baseline and at the end of the intervention. During the study period, a total of 172 IBS patients were enrolled in the observational study, while 35 IBS patients completed the one-month LFD intervention, and 41 IBS patients receiving standard care constituted the concurrent control group for the interventional analysis. Stool samples collected pre-intervention were analyzed to examine baseline gut microbiota, enabling comparisons between eventual responders and non-responders.

2.3. INTERVENTIONAL DIET

A low FODMAP diet involves the restriction of foods containing fermentable oligosaccharides, monosaccharides, disaccharides, and polyols.[8] Patients in the LFD group received instructional manuals from nutritionists and were required to submit a weekly food diary (capturing daily intake) and food photographs to researchers via an online platform. If a participant failed to adhere to the suggested food list more than twice within a week, they were withdrawn from the study. The control group received standard care. The contents of the LFD were assessed using the LFD score.[20]

2.4. DATA COLLECTION AND QUESTIONNAIRES

We recorded demographic data, including age, sex, and IBS duration, from all participants. Gastrointestinal symptoms were measured at baseline and at the end of the intervention using the IBS Symptom Severity Scale (IBS-SSS). The severity of IBS symptoms was categorized as mild (scores 75–175), moderate (scores 176–300), or severe (scores > 300).[21] Additionally, participants completed the IBS Quality

of Life Measure (IBS-QoL) as a secondary outcome measure.[22] The Hamilton Anxiety Rating Scale (HAMA) was used to evaluate the severity of anxiety symptoms. The HAMA consists of 14 items scored on a five-point scale, with a total score range of 0–56.[23] A score ⩽7 indicates no anxiety, 8–17 indicates mild anxiety, 18–24 indicates mild to moderate anxiety, and ⩾25 indicates severe anxiety.[23]

2.5. EXPLORATORY ANALYSES

To identify potential microbial signatures associated with differential response to the LFD, we performed 16S rRNA sequencing on pre-intervention stool samples. This exploratory analysis focused on a subset of 11 patients (responders = 5, non-responders = 6) whose clinical outcomes were predefined and for whom baseline samples were available, allowing comparisons of baseline microbiota between response groups.

We randomly selected six patients from the pool of 25 overall responders, ensuring they had complete baseline clinical data and a pre-intervention stool sample available for analysis. However, one stool sample was not qualified for 16S rRNA sequencing. We included all six non-responders from the overall cohort who had both complete data and a pre-intervention stool sample available (from the total of 10 non-responders).

Response to the LFD was defined as a reduction of more than 50 points in the IBS-SSS score after the one-month intervention. Stool samples collected before the LFD intervention were immediately frozen and stored at −80 °C in 2 mL screw-cap cryovials until further analysis. DNA extraction kits—OMEGA Soil DNA Kit (D5625-02, Omega Bio-tek, Inc., USA, OMEGA Water DNA Kit (D5525-01,Omega Bio-tek, Inc., USA), and OMEGA Stool DNA Kit (D4015-02, mega Bio-tek, Inc., USA)—were used for different sample types to ensure optimal DNA extraction efficiency and quality. The PCR primers targeted conserved regions flanking variable regions of the bacterial 16S rRNA gene and the fungal ITS2 region. After 35 cycles of polymerase chain reaction (PCR), sequencing adapters and barcodes were added for amplification. PCR products were detected by 1.5% agarose gel electrophoresis. Target fragments were recovered using the AxyPrep PCR Cleanup Kit (AP-PCR-250G, Axygen, USA) and further purified using the Quant-iT PicoGreen dsDNA Assay Kit (P7589, Invitrogen, USA). The library was quantified using the Promega QuantiFluor fluorescence quantification system. The pooled library was then loaded onto the Illumina platform using a paired-end sequencing protocol (2 × 250 bp). Paired-end reads were assigned to samples based on their unique barcodes and truncated by removing the barcode and primer sequences. Paired-end reads were merged using FLASH (v1.2.8, Tanja Magoc & Steven L. Salzberg, USA) for 16S and PEAR (v0.9.6, Jiajie Zhang, Germany) for ITS2.

Low-quality reads (quality scores <20), short reads (<100 bp), and reads containing more than 5% “N” bases were filtered using the sliding-window algorithm in fqtrim (v0.94, Geo Pertea, USA). Quality filtering was performed to obtain high-quality, clean tags according to fqtrim guidelines. Chimeric sequences were filtered using Vsearch software (v2.3.4, Torbjørn Rognes, Norway). After dereplication using DADA2 (v1.28.0, Benjamin Callahan, USA), feature tables and feature sequences were obtained. Alpha diversity and beta diversity were calculated using QIIME2 (v2019.7, Gregory Caporaso, USA), where the same number of sequences were randomly selected by reducing the total number of sequences to match the sample with the fewest sequences, and relative abundance (bacteria count/total count) was used for taxonomy assignments. Alpha and beta diversity analyses were performed using QIIME2, and visualizations were created using R (v3.5.2, R Core Team, New Zealand). Species annotation was performed using BLAST (v2.15.0, Stephen Altschul, USA), and species alignment was based on the SILVA and NT-16S databases.

2.6. STATISTICAL ANALYSIS

Descriptive data were presented as categorical variables (relative frequencies, %) and continuous variables (mean ± standard deviation for normally distributed data, or median [interquartile range] for abnormally distributed data). Normality was evaluated using graphical methods and the Kolmogorov–Smirnov test. Variables that did not meet the normality assumption (K-S, $p < 0.05$) were analyzed using non-parametric methods. Categorical variables were compared using the chi-square test or Fisher’s exact test, as appropriate. Independent-samples and paired-samples *t*-tests were used to examine differences in normally distributed continuous variables. For comparisons involving three or more independent groups, one-way analysis of variance (ANOVA) was used, followed by appropriate post-hoc tests (Bonferroni) when significant main effects were found.

For non-normally distributed or ordinal data, the Kruskal–Wallis *H* test was applied for comparisons of three or more independent groups. Two-tailed *p*-values of ⩽0.05 were considered statistically significant. Relationships between continuous variables were assessed using Spearman’s rank correlation coefficient, selected for its robustness to non-normality. Multiple logistic regression was performed to identify factors associated with treatment efficacy (defined as a reduction of more than 50 points in the IBS-SSS score). Variable selection was based on a backward stepwise elimination procedure using the likelihood ratio test. The final model’s goodness-of-fit was evaluated using the Hosmer–Lemeshow test, and assumptions were checked for multicollinearity using variance inflation factors and influential observations.

Results are reported as odds ratios with 95% confidence intervals. A multiple linear regression analysis was applied to compare post-intervention outcomes while controlling for baseline confounders. The post-intervention IBS-SSS score was treated as a continuous variable. The model incorporated the following covariates: group, age, gender, IBS subtype, baseline IBS-SSS score, and baseline HAMA score. All covariates were entered using the forced entry method. All statistical analyses were conducted using IBM SPSS Statistics (v27.0, IBM Corp., USA) and GraphPad Prism (v10.0.0, GraphPad Software, USA).

3. RESULTS

3.1. BASELINE CHARACTERISTICS OF THE OBSERVATIONAL COHORT

Of the 177 IBS patients prospectively enrolled, five were excluded due to incomplete demographic data, resulting in an analytical cohort of 172 participants. This cohort was predominantly comprised of patients with IBS-D and comorbid anxiety. While no significant differences were found in age or gender among the anxiety severity groups, the distribution of IBS subtypes varied significantly. Specifically, the

mild anxiety group had a significantly higher prevalence of IBS-D than the moderate-to-severe anxiety groups (Table 1).

3.2. ANXIETY SEVERITY POSITIVELY CORRELATED WITH IBS SYMPTOM SEVERITY

Among the 172 participants, 54 were assessed as having mild anxiety, 22 with mild-to-moderate anxiety, 31 with severe anxiety, and the remaining participants were classified as non-anxious (Table 1). A range of clinical data, including lactulose breath test (LBT) results, was collected. No significant differences were observed in the positive LBT rate or the frequency of therapeutic drug use between groups, except for antispasmodics (Table 1). Nevertheless, the Kruskal–Wallis test revealed significant differences in IBS-SSS ($p < 0.001$) and IBS-QoL ($p < 0.001$) scores. Post-hoc analysis using the Bonferroni test showed that the severe anxiety group had significantly higher IBS-SSS scores compared to the non-anxious group ($p < 0.001$) and the mild anxiety group ($p = 0.032$) (Figure 1). Similarly, the severe anxiety group exhibited the highest IBS-QoL scores (Figure 1).

Correlation analyses demonstrated a significant association between HAMA anxiety scores and both IBS-SSS ($r = 0.34$, $p < 0.0001$) and IBS-QoL ($r = 0.46$, $p < 0.0001$) (Figure 2A and 2B). Multiple logistic regression identified rifaximin as the only effective treatment for IBS patients (Figure 2C). Additionally, the moderate-to-severe anxiety group exhibited a higher proportion of IBS-C and IBS-M subtypes and a lower proportion of IBS-D and IBS-U subtypes. LBT, used to diagnose small intestinal bacterial overgrowth associated with IBS,[24] revealed no significant relationship between LBT results and IBS-SSS scores (Figure 2D). A Mediterranean diet, known for its positive effects on cardiovascular health, obesity, and mood modulation, was assessed for its impact on IBS symptoms.[25] However, our study found no significant therapeutic effects of this diet on either clinical or mental health symptoms of IBS (Figure 2D).

3.3. LOW FODMAP DIET AS AN EFFECTIVE TREATMENT FOR IRRITABLE BOWEL SYNDROME PATIENTS

A pilot study was conducted to explore the efficacy of dietary intervention on both clinical symptoms and mental health in IBS patients. A total of 35 patients were prospectively recruited for the interventional study, with a mean age of 28.18 ± 5.88 years. A total of 41 patients were included in the control group, with a mean age of 31.59 ± 10.31 years. The majority of participants were male (91.4% in the LFD group and 85.4% in the control group). Baseline characteristics showed some differences between groups, particularly in anxiety and dietary scores (Tables 2 and **S1**). Based on the Rome IV criteria, 88.6% of the LFD group had IBS-D, 2.9% had IBS-C, 2.9% had IBS-M, and 5.7% had IBS-U (Table 2). Baseline IBS-SSS and IBS-QoL scores were 350.29 ± 93.10 and 6.44 ± 1.58, respectively (Table 2).

According to the HAMA questionnaire, the baseline anxiety scores of the two groups were 20.4 ± 5.0 (LFD group) and 25.71 ± 7.92 (control group) (Table 2). The LFD intervention lasted four weeks, with an average LFD score of 4.83 ± 3.29, indicating good dietary adherence. Anxiety scores decreased significantly after the intervention (5.74 ± 1.88 vs. 20.4 ± 5.0, $p < 0.001$; Table 3). The proportion of patients in the LFD group achieving a ⩾50% reduction in HAMA scores was 94.29%, while no patients showed a reduction in HAMA scores in the control group (**Figure S1**).

Table 1. Clinical characteristics of patients in the observational study

Characteristics	Non-anxiety group (*n* = 65; *n* [%])	Mild anxiety group (*n* = 54; *n* [%])	Mild to moderate anxiety group (*n* = 22; *n* [%])	Severe anxiety group (*n* = 31; *n* [%])	*p*-value	Effect size
Age (year)	29 (10)	29 (11)	26 (9)	31 (15)	0.316	0.015
Male	55 (84.6)	49 (90.7)	20 (90.9)	26(83.9)	0.698	0.062
IBS type						
IBS with diarrhea	44 (67.7)	43 (79.6)	17 (77.3)	20 (64.5)	<0.001	0.186
IBS with constipation	2 (3.1)	5 (9.3)	3 (13.6)	6 (19.4)		
IBS with mixed stool patterns	1 (1.5)	1 (1.9)	0 (0)	5 (16.1)		
Unclassified IBS	18 (27.7)	5 (9.3)	2 (9.1)	0 (0)		
IBS Symptom Severity Scale	280 (170)	300 (105)	340 (135)	400 (160)	<0.001	0.084
IBS-Quality of Life Measure	5 (3)	6 (2)	7 (3)	7 (1.5)	<0.001	0.101
Positive LBT	18 (27.7)	21 (38.9)	6 (27.3)	12 (38.7)	0.666	0.051
Medications						
PPI	2 (3.1)	5 (9.3)	3 (13.6)	2 (6.5)	0.275	0.078
Probiotics	7 (10.8)	10 (18.5)	5 (22.7)	8 (25.8)	0.272	0.079
Antibiotics	4 (6.2)	2 (3.7)	2 (9.1)	2 (6.5)	0.778	0.041
Bismuth	1 (1.5)	1 (1.9)	1 (4.5)	1 (3.2)	0.664	0.043
Antispasmodics	0 (0)	2 (3.7)	3 (13.6)	2 (6.5)	0.018	0.137

Note: Data are presented as mean (standard deviation) for continuous variables and *n* (%) for categorical variables.
Abbreviations: IBS: Irritable bowel syndrome; LBT: Lactulose breath test; PPI: Proton pump inhibitor.

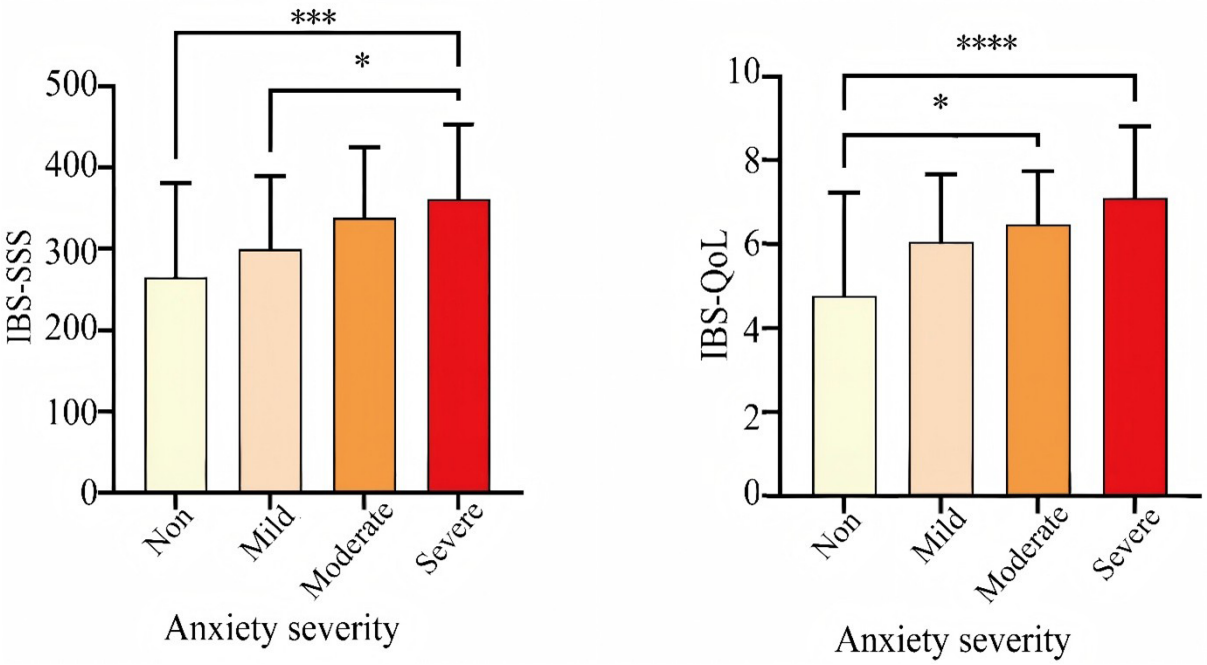

Figure 1. Distribution of IBS-SSS and IBS-QoL scores of IBS patients stratified by anxiety severity. *p < 0.05, ***p < 0.001, and ****p < 0.0001 indicate statistical significance.
Abbreviations: IBS: Irritable bowel syndrome; IBS-SSS: Irritable Bowel Syndrome Symptom Severity Scale; IBS-QoL: Irritable Bowel Syndrome Quality of Life.

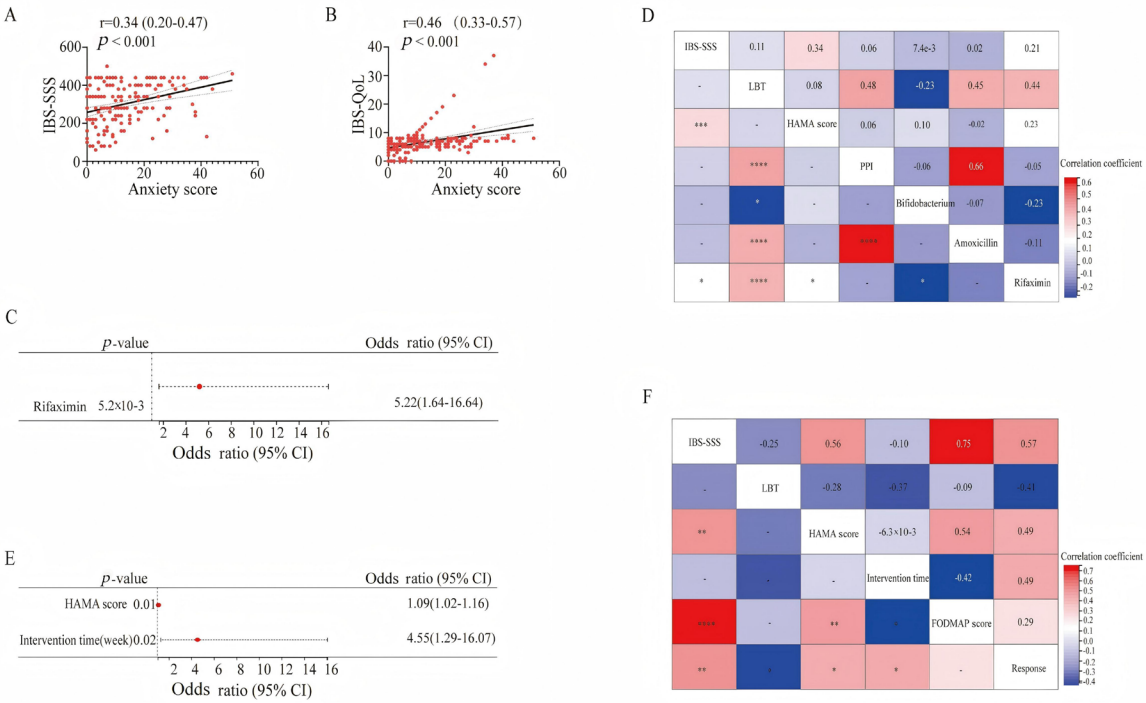

Figure 2. Clinical profiles of two cohorts of IBS patients. (A, B) Positive correlations were observed between (A) IBS-SSS scores and HAMA scores and (B) IBS-QoL scores and HAMA scores. (C) Multiple logistic regression analysis of IBS patients receiving conventional therapy identified rifaximin as the only drug with significant efficacy. (D) Correlation analysis in the observational cohort of IBS patients revealed no direct relationship between LBT results and IBS symptom severity. (E) Multiple logistic regression analysis in the interventional cohort revealed that intervention duration was the sole factor significantly associated with treatment efficacy. (F) Correlation analysis in the interventional cohort demonstrated that FODMAP scores were positively correlated with IBS symptom severity. *p < 0.05, **p < 0.01, ***p < 0.001, and ****p < 0.0001 indicate statistical significance.
Abbreviations: FODMAP: Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; HAMA: Hamilton Anxiety Rating Scale; IBS: Irritable bowel syndrome; IBS-SSS: Irritable Bowel Syndrome Symptom Severity Scale; IBS-QoL: Irritable Bowel Syndrome Quality of Life.

Table 2. Baseline characteristics of the interventional study

Characteristic	LFD group	Control group	*p*-value	Effect size
Age (year)	28.18 (5.88)	31.59 (10.31)	0.351	0.38
Male	32 (91.4)	41 (85.4)	0.514	0.09
IBS type				
IBS with diarrhea	31 (88.6)	28 (68.3)	0.072	0.30
IBS with constipation	1 (2.9)	8 (19.5)	0.034	
IBS with mixed stool patterns	1 (2.9)	4 (9.8)	0.375	
Unclassified IBS	2 (5.7)	1 (2.4)	0.569	
Duration (year)	2.07 (2.09)	2.59 (3.68)	0.567	0.17
IBS Symptom Severity Scale	350.29 (93.10)	361.7 (80.31)	0.567	0.13
IBS-Quality of Life Measure	6.44 (1.58)	6.85 (1.53)	0.345	0.26
Anxiety score	20.4 (5.0)	25.71 (7.92)	<0.01	0.81
Medications				
PPI	6 (17.1)	7 (17.1)	1.000	0.00
Bismuth	1 (2.9)	4 (9.8)	0.375	0.14
Antispasmodics	2 (5.7)	4 (9.8)	0.678	0.08
LFD score	12.31 (1.71)	6.42 (2.41)	<0.001	2.76

Note: Data are presented as mean (standard deviation) for continuous variables and *n* (%) for categorical variables.
Abbreviations: IBS: Irritable bowel syndrome; LFD: Low FODMAP diet; PPI: Proton pump inhibitor.

Table 3. Changes in irritable bowel syndrome severity and anxiety before and after dietary intervention

Assessment	IBS Symptom Severity Scale	IBS-Quality of Life Measure	Anxiety score
Before	350.29 (93.10)	6.44 (1.58)	20.4 (5.0)
After	241.82 (80.21)	4.42 (1.79)	5.74 (1.88)
p-value	<0.001	<0.001	<0.001
Effect size	1.30	1.28	3.03

Abbreviation: IBS: Irritable bowel syndrome.

Furthermore, IBS-SSS and IBS-QoL scores improved significantly after four weeks of LFD intervention compared to baseline values (241.82 ± 80.21 vs. 350.29 ± 93.10, $p < 0.001$; 4.42 ± 1.79 vs 6.44 ± 1.58, $p < 0.001$, respectively; Table 3). A total of 25 patients out of the total 35 participants (25/35, 71.4%) responded to the intervention, defined as a reduction of more than 50 points in IBS-SSS scores, and the remaining 10 patients (10/35, 28.6%) were considered non-responders.

Multiple logistic regression revealed that intervention duration was the only factor significantly associated with efficacy (Figure 2E). Higher FODMAP scores correlated with greater IBS severity, and anxiety severity was linked to LFD response (Figure 2F). In contrast, control patients showed symptom worsening at follow-up (Table 4). In addition, a multiple linear regression analysis was performed to examine the effect of LFD (Table 5). The result showed that LFD intervention remained an independent and significant factor for the marked reduction in post-intervention IBS-SSS scores, after adjusting for baseline confounding factors such as HAMA score. The overall model fit was excellent, explaining 72% of the variance in the outcome ($R^2 = 0.72$). The changes in HAMA scores for each patient are shown in **Figure S1**.

3.4. GUT MICROBIOTA COMPOSITION ALTERED AFTER LFD INTERVENTION

To assess whether gut microbiota composition was associated with clinical response to LFD, baseline stool samples from 11 patients (responders = 5, non-responders = 6) underwent 16S rRNA sequencing. While no significant differences were observed in α-diversity (Shannon index, Figure 3A) or β-diversity (unweighted UniFrac and Bray-Curtis distances, Figure 3B), the taxonomic composition at the genus level differed markedly between groups (Figure 3C and 3D). Notably, responders exhibited higher abundances of *Parabacteroides* ($p = 0.01$), *Lactobacillus* ($p = 0.03$), *Citrobacter* ($p = 0.03$), *Enterobacter* ($p = 0.03$), *Klebsiella* ($p = 0.04$), *Eubacterium ventriosum* ($p < 0.05$), and *Holdemania* ($p < 0.05$) (Figure 3D). Furthermore, although not statistically significant due to the limited sample size, we observed trends suggesting a negative correlation between *Dialister* abundance and IBS-SSS scores, and a positive correlation between *Erysipelotrichaceae* UCG-003 abundance and IBS-SSS scores (Figure 3E).

4. DISCUSSION

Irritable bowel syndrome is a prevalent disorder of gut–brain interaction, with approximately 39% of patients reporting symptoms of anxiety.[26] Evidence has confirmed the pivotal role of the gut–brain axis in gastrointestinal disorders.[27] The gut–brain axis is considered a key mediator in the pathophysiology of IBS, and treatments targeting central nervous system modulation have demonstrated efficacy.[28] An integral component of this axis is the gut microbiota, which influences key IBS features such as gut motility and visceral sensitivity, and can modulate brain activity

Table 4. Changes in irritable bowel syndrome severity and anxiety in the control group

Assessment	IBS Symptom Severity Scale	IBS-Quality of Life Measure	Anxiety score
Before	361.7 (80.31)	6.85 (1.53)	25.71 (7.92)
After	390.7 (51.59)	7.61 (1.50)	28.44 (6.76)
p-value	>0.05	<0.05	>0.05
Effect size	−0.39	−0.50	−0.38

Abbreviation: IBS: Irritable bowel syndrome.

Table 5. Multiple linear regression analysis comparing post-intervention outcomes between the two groups

Covariates	*B*	*p*-value	95% CI
Intercept	229.03	<0.001	(133.37, 324.69)
Baseline IBS-SSS score	0.31	<0.01	(0.09, 0.53)
Baseline HAMA score	−1.20	0.23	(−3.16, 0.76)
Gender	−10.75	0.63	(−54.66, 33.16)
Age	1.34	0.10	(−0.26, 2.95)
IBS subtype	−16.08	0.33	(−48.68, 16.52)
Group (LFD/control)	−150.54	<0.001	(−177.80, −123.28)

Note: Adjusted $R^2 = 0.72$.
Abbreviations: CI: Confidence interval; HAMA: Hamilton Anxiety Rating Scale; IBS: Irritable bowel syndrome; IBS-SSS: Irritable Bowel Syndrome Symptom Severity Scale; LFD: Low FODMAP diet.

through microbial metabolites, including tryptophan derivatives and short-chain fatty acids (SCFAs).[29]

Notably, the gut microbiome itself differs between anxious and non-anxious IBS patients. For instance, anxious patients tend to exhibit higher abundances of *Clostridioides* and *Bacteroides* and lower levels of *Bifidobacterium* and *Faecalibacterium* compared to their non-anxious counterparts.[30] Our findings align with this complex interplay, demonstrating a significant positive correlation between anxiety (HAMA) and symptom severity (IBS-SSS) scores. Collectively, these findings suggest that the LFD is an effective intervention for improving IBS gastrointestinal symptoms and anxiety status, and that microbiome analysis suggests that the gut microbiota may play a role in mediating dietary responses. However, as our observational data cannot determine causality, they underscore the bidirectional and multifaceted nature of the gut–brain axis in IBS, highlighting the need for further mechanistic evidence.

Conventional pharmacological treatments for IBS often yield suboptimal outcomes, with rifaximin being a notable exception. Beyond pharmaceuticals, alternative approaches show promise. For instance, the Japanese traditional medicine *Kampo* has emerged as a potential therapy for IBS-D, though its widespread clinical application awaits validation through randomized controlled trials.[31] Recently, a cross-sectional study revealed a significantly higher proportion of eating disorders in IBS patients, with higher levels of anxiety and depression.[32] In this context, dietary modification remains a cornerstone in IBS management, including symptom-directed recommendations such as adjusting soluble fiber intake and restricting caffeine and alcohol consumption.[33] LFD works by reducing or replacing six categories of fermentable carbohydrates, addressing their three primary mechanisms of symptom induction in IBS: poor absorption in the small intestine, osmotic activity, and rapid bacterial fermentation.[34] Despite its established efficacy for gastrointestinal symptoms, the role of LFD as a standard therapy—particularly for psychological comorbidities—remains debated[12,35,36]. While some meta-analyses suggest its effect on anxiety and depression may be limited[12], other studies, such as the work by Eswaran *et al.*,[37] report that a four-week LFD intervention can alleviate anxiety, with effects being most pronounced in the IBS-D subtype.[37,38]

Our findings contribute to this discussion by demonstrating that LFD significantly improved not only IBS-SSS and IBS-QoL scores but also anxiety symptoms. Potential mechanisms underlying these broad benefits are being elucidated. Prospero *et al.*[36] showed that a 12-week LFD improved intestinal mucosal integrity and significantly decreased interleukin-6, lipopolysaccharide levels, and fermentative dysbiosis. Furthermore, preliminary evidence suggests that the gut microbiota may mediate the therapeutic effects of LFD.[39]. It has been proposed that LFD's positive impact on psychological well-being could stem from its ability to modulate immune responses, enhance gut barrier function, and correct microbial dysbiosis.[40]

The contribution of gut microbiota to dietary interventions remains debated. While some studies report that LFD reduces the abundance of specific taxa like *Bifidobacterium* and *Actinobacteria*, others observe a broader shift toward a "healthier" profile, characterized by an increased *Bacteroidetes*/*Firmicutes* ratio.[41] Notably, patients whose baseline microbiota are enriched in Firmicutes—a phylum involved in carbohydrate metabolism—often show better clinical responses to LFD,[19] and metabolic subtypes characterized by high SCFA levels have been linked to greater dietary efficacy.[18] However, some studies contradict these findings. In our observational study, probiotic administration (primarily *Bifidobacterium*) was not associated with a significant improvement in IBS-SSS scores. This aligns with findings from Wilson *et al.*,[42] who found no difference in the absolute abundance of fecal *Bifidobacterium* between responders and non-responders either at baseline or after four weeks of LFD intervention. The observational data and literature together suggest that administration of *Bifidobacterium* alone may not be a primary determinant of response in this context.

Although no significant changes in β-diversity were observed between responders and non-responders in our

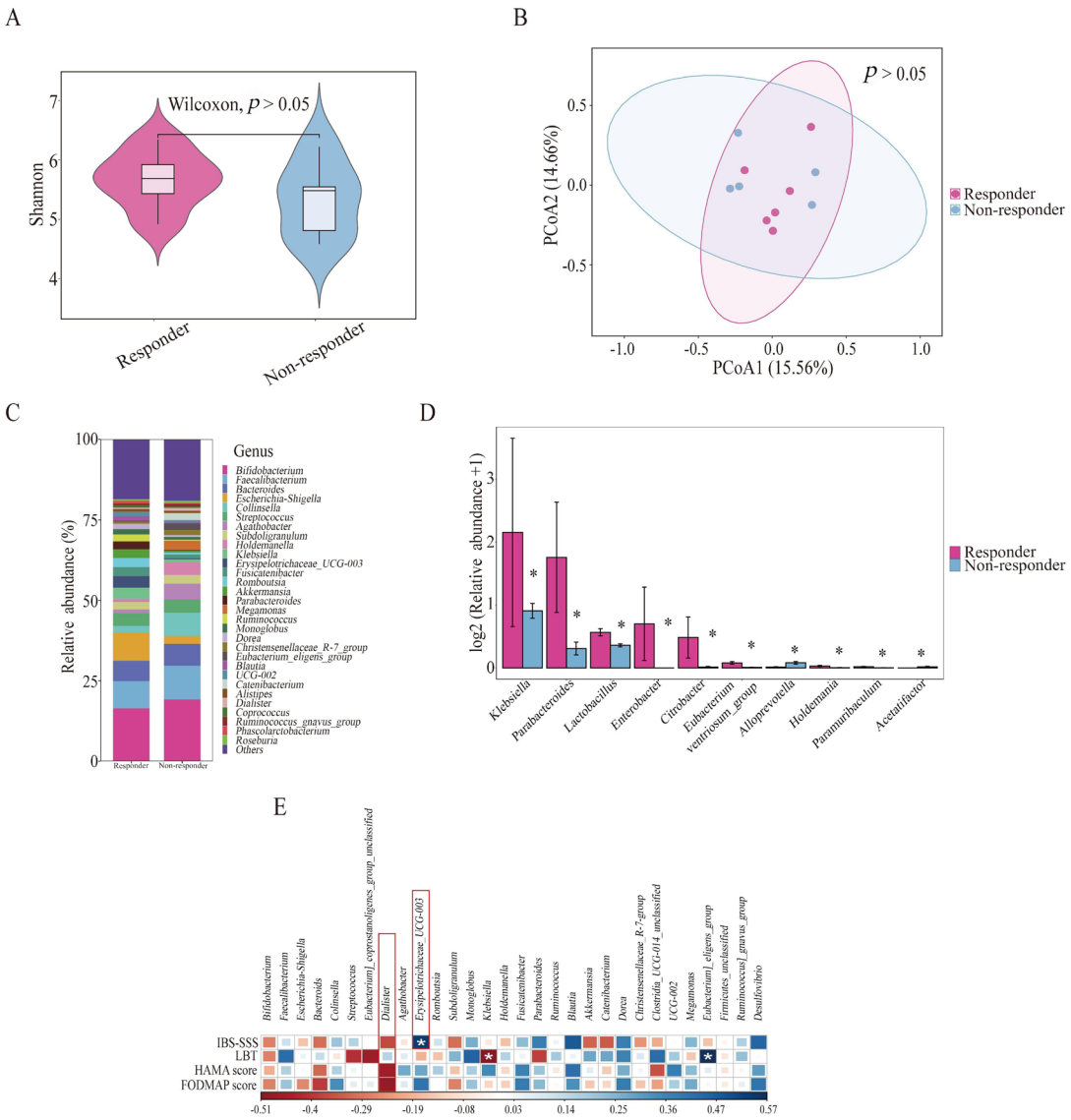

Figure 3. Gut microbiota composition is altered after low FODMAP diet intervention. (A) Shannon index revealed no significant differences in α-diversity between responders and non-responders ($p > 0.05$). (B) Principal coordinates analysis revealed no significant differences in β-diversity between responders and non-responders. (C) The top 30 genera differed between responders and non-responders. (D) Analysis of significantly different taxa between responders and non-responders (Mann–Whitney *U* test, $p < 0.05$). (E) Heatmap showing Spearman correlation coefficients between selected clinical variables and gut bacterial abundance in IBS patients receiving LFD. *$p < 0.05$ indicates statistical significance.

Abbreviations: FODMAP: Fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; HAMA: Hamilton Anxiety Rating Scale; IBS: Irritable bowel syndrome; IBS-SSS: Irritable Bowel Syndrome Symptom Severity Scale; LBT: Lactulose breath test.

study, the microbiota composition was markedly different. Specifically, LFD increased the abundance of *Lactobacillus*, a probiotic known to benefit IBS patients and alleviate anxiety.[43,44] Lacidophilin tablets containing lactic acid and seven SCFAs have been shown to improve anxiety- and depression-like behavior in IBS rats.[45] In addition, *Lactobacillus* species are known to produce γ-aminobutyric acid, which can ameliorate depression and anxiety.[46] Our study also shows that *Parabacteroides* was enriched in responders. Certain *Parabacteroides* species are associated with the production of SCFAs like propionate and butyrate, which can modulate systemic inflammation, strengthen the gut barrier, and influence central nervous system function via neuroimmune and humoral pathways.[47] Therefore, future metabolomic studies are needed to directly measure these potential mediators, including SCFAs and tryptophan metabolites, in the context of LFD intervention, to establish a clearer mechanistic link between diet-induced microbial shifts and anxiety outcomes in IBS.

While LFD has demonstrated efficacy comparable to conventional therapies in improving IBS symptoms, its long-term sustainability poses a significant challenge. The methodology for reintroducing FODMAPs remains inadequately studied and standardized. Evidence indicates that fructans and mannitol are the most common triggers for symptom recurrence following a six-week LFD

intervention.[20] Consequently, expert guidance is crucial for successful implementation. A recent review underscores the essential role of registered dietitians in managing the individualized three-phase FODMAP diet, while noting that structured self-guided programs or specialized meal services may serve as alternatives when professional support is not accessible.[35]

Several studies have reported a positive relationship between LBT results and gut symptoms, such as abdominal bloating, with positive LBTs being more prevalent in IBS-C patients.[48] In contrast, our study found no significant association between positive LBTs and IBS severity. This discrepancy may be attributed to the relatively small sample size and the predominance of IBS-D patients in our cohort. Additionally, rifaximin, which is often used to treat patients with positive LBT results, was associated with reductions in both HAMA and IBS-SSS scores in our study, further highlighting the involvement of gut microbial factors in the pathophysiology of IBS.

This study has several limitations that should be considered when interpreting the results. First, the predominance of male participants contrasts with the typical female preponderance in IBS epidemiology, which may introduce selection bias and limit the generalizability of our findings to female patients. Second, the strict exclusion criteria applied to the interventional cohort, while necessary for protocol control, may restrict the applicability of our conclusions to the broader, more heterogeneous IBS population seen in clinical practice. Third, the relatively modest sample size, particularly in the exploratory microbiome analysis, reduces statistical power and may have limited our ability to detect subtle but potentially important associations. Fourth, the non-randomized design and the absence of blinding mean that participants in the LFD group were aware of their dietary intervention; this factor, coupled with observed baseline differences, may introduce expectation bias and confound the interpretation of between-group comparisons. Finally, the four-week intervention period is insufficient to evaluate the long-term sustainability, safety, and efficacy of the LFD. Future rigorous investigations, including large-scale, randomized, double-blind, placebo-controlled trials with extended follow-up periods, are needed to confirm our findings and evaluate long-term dietary management strategies, including FODMAP reintroduction protocols.

5. CONCLUSION

In summary, this work highlights two key clinical insights: the substantial burden of untreated anxiety in IBS and the potential of LFD as an emergent therapeutic strategy that concurrently improves physical and mental health outcomes. However, LFD management requires dietetic support, patient adherence, and consideration of cost-effectiveness. Unlike conventional anxiolytics, LFD offers a distinct, microbiome-modulating approach that may be preferable for select patients. Our exploratory data further suggest that specific gut microbes, such as *Klebsiella*, *Parabacteroides*, and *Lactobacillus*, could be relevant to the therapeutic response. Given the limitations of the present study, these findings warrant cautious interpretation and should be validated in larger, randomized controlled trials.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supervision: Wei Chen, Fangyu Wang, Lei Ye
Validation: Liuying Li, Heng Lu
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Writing–review & editing: Lei Ye, Hui Shi

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Jinling Hospital of Nanjing University (protocol code: 2023DZKY-023-01).

CONSENT FOR PUBLICATION

Written informed consent was obtained from all the participants prior to enrollment.

DATA AVAILABILITY STATEMENT

Raw 16S rRNA sequencing data were deposited in the National Center for Biotechnology Information (NCBI) Sequence Read Archive database (accession number: PRJA1068549).

ADDITIONAL DISCLOSURE

The authors utilized ChatGPT 5.0 for language polishing during manuscript preparation. AI-edited sections underwent human review and proofreading to ensure content accuracy. The authors assume responsibility for this process.

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