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A Multicenter Randomized Controlled Trial of Microbiome-Based Artificial Intelligence-Assisted Personalized Diet vs Low-Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols Diet: A Novel Approach for the Management of Irritable Bowel Syndrome

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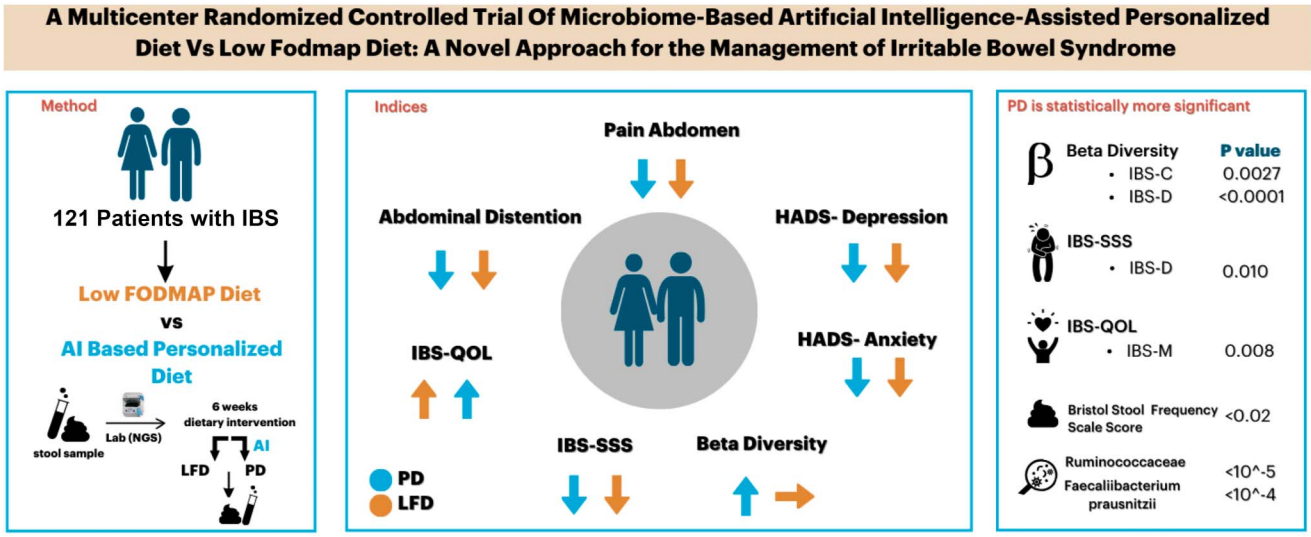
INTRODUCTION: **Personalized management strategies are pivotal in addressing irritable bowel syndrome (IBS). This multicenter randomized controlled trial focuses on comparing the efficacy of a microbiome-based artificial intelligence-assisted personalized diet (PD) with a low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet (FODMAP) for IBS management.**



Tunali et al. *Am J Gastroenterol. 2024* doi:10.14309/ajg.0000000000002862

AJG The American Journal of GASTROENTEROLOGY

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Received December 20, 2023; accepted April 26, 2024; published online May 8, 2024

METHODS: **One hundred twenty-one patients participated, with 70 assigned to the PD group and 51 to the FODMAP diet group. IBS subtypes, demographics, symptom severity (IBS-SSS), anxiety, depression, and quality of life (IBS-QOL) were evaluated. Both interventions spanned 6 weeks. The trial's primary outcome was the within-individual difference in IBS-SSS compared between intervention groups.**

RESULTS: **For the primary outcome, there was a change in IBS-SSS of −112.7 for those in the PD group vs −99.9 for those in the FODMAP diet group ($P = 0.29$). Significant improvement occurred in IBS-SSS scores ($P < 0.001$), frequency ($P < 0.001$), abdominal distension ($P < 0.001$), and life interference ($P < 0.001$) in both groups. In addition, there were significant improvements in anxiety levels and IBS-QOL scores for both groups ($P < 0.001$). Importantly, PD was effective in reducing IBS SSS scores across all IBS subtypes IBS-Constipation (IBS-C; $P < 0.001$), IBS-Diarrhea (IBS-D; $P = 0.01$), and IBS-Mixed (IBS-M; $P < 0.001$) while FODMAP diet exhibited comparable improvements in IBS-C ($P = 0.004$) and IBS-M ($P < 0.001$). PD intervention significantly improved IBS-QOL scores for all subtypes (IBS-C [$P < 0.001$], IBS-D [$P < 0.001$], and IBS-M [$P = 0.008$]) while the FODMAP diet did so for the IBS-C ($P = 0.004$) and IBS-D ($P = 0.022$). Notably, PD intervention led to significant microbiome diversity shifts ($P < 0.05$) and taxa alterations compared with FODMAP diet.**

DISCUSSION: **The artificial intelligence-assisted PD emerges as a promising approach for comprehensive IBS management. With its ability to address individual variation, the PD approach demonstrates significant symptom relief, enhanced QOL, and notable diversity shifts in the gut microbiome, making it a valuable strategy in the evolving landscape of IBS care.**

KEYWORDS: irritable bowel syndrome; personalized diet; microbiome; artificial intelligence

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D284

Am J Gastroenterol 2024;00:1–12. https://doi.org/10.14309/ajg.0000000000002862

INTRODUCTION

Irritable bowel syndrome (IBS) is a complex and prevalent functional gastrointestinal disorder characterized by recurrent abdominal pain, altered bowel habits, and bloating (1). With a global prevalence of approximately 4.1%, this prevalent gastrointestinal disorder, along with its associated comorbidities, presents a significant challenge for both individuals and societies (2). The symptoms primarily related to bowel discomfort and pain not only pose a serious threat to public health but also have a profound impact on individuals' quality of life (QOL). Moreover, this disorder results in substantial economic burdens, including expenses incurred for health care and productivity losses due to absenteeism (3). The pathophysiology of IBS is multifactorial, involving dysregulation of gut-brain interactions, altered gut motility, visceral hypersensitivity, and dysbiosis of the gut microbiome (4).

In recent years, emerging evidence suggests that alterations in the gut microbiome composition and function play a crucial role in the development and symptomatology of IBS (5). The gut microbiome represents a diverse ecosystem of microorganisms residing in the gastrointestinal tract, which interact with the host immune system, modulate gut barrier function, and contribute to the metabolism of dietary substrates (6). Consequently, interventions targeting the gut microbiome have gained considerable attention as a potential therapeutic approach for IBS.

Among the various dietary interventions explored in IBS, low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet has shown promising results in reducing symptoms and improving overall well-being (7). The FODMAP diet involves the restriction of fermentable carbohydrates that are poorly absorbed in the small intestine, thus reducing their availability for fermentation by colonic bacteria (8).

Studies have shown that long-term adherence to a strict FODMAP diet may lead to a reduction in the abundance and diversity of beneficial microbial species, potentially compromising gut microbiome health (7–9). This microbial dysbiosis associated with the FODMAP diet may have broader implications beyond symptom relief, as alterations in the gut microbiome have been linked to various aspects of host health, including immune function, metabolism, and mental well-being (10–12).

A microbiome-based personalized diet (PD) shows promise as a novel therapeutic approach to address IBS symptoms while prioritizing gut microbiome diversity and health, aiming to overcome the limitations and potential negative effects of the FODMAP diet (13). By integrating microbiome analysis and artificial intelligence (AI) algorithms, personalized dietary recommendations can be tailored to an individual's unique gut microbiome composition, aiming to restore and enhance microbial diversity and function (14,15). The microbiome-based PD approach acknowledges the complex interplay among diet, the gut microbiome, and host health, tailoring dietary interventions to individual gut microbial profiles to enhance the growth of beneficial bacteria and optimize the microbial community structure (16).

In this multicenter randomized controlled trial, we aimed to compare the efficacy and feasibility of a microbiome-based AI-assisted PD with the FODMAP diet in the management of IBS symptoms. By integrating microbiome profiling and AI algorithms, we hypothesized that the PD intervention would lead to superior symptom improvement and overall patient satisfaction compared with the FODMAP diet alone. In addition, we evaluated changes in the gut microbiome composition as a secondary outcome, exploring potential mechanistic links between dietary interventions and clinical responses.

MATERIALS AND METHODS

Study cohort

In this multicenter, parallel, randomized, controlled, double-blind, comparative study, we enrolled adult patients (aged 18–65 years) who met the Rome IV criteria for IBS from the gastroenterology outpatient clinics of 4 different centers located in 3 different cities (Istanbul, Izmir, and Kayseri). The exclusion criteria included the presence of severe chronic diseases (such as cancer, diabetes, cardiovascular diseases, liver diseases, and neurological disorders), psychiatric comorbidity, or any other gastrointestinal disease other than IBS (e.g., inflammatory bowel disease, malabsorption of any macronutrient, intestinal resection, or celiac disease) that could potentially affect the gut microbiome. Patients who were following excessively restrictive diets (e.g., low-FODMAP, gluten-free, vegan, and lactose-free diet) were also excluded. Individuals who had undergone colonoscopy or had used antibiotics within the past 4 weeks were not included in the study. Probiotics, prebiotics, and fecal assistance products were not allowed during the study period and were weekly monitored by phone calls. The study was conducted between August 2022 and May 2023, and all patients received specific verbal and written information about the study before providing their written consent to participate. We used the CONSORT reporting guidelines (17). The study protocol was approved by the regional ethical review boards. This trial is registered on ClinicalTrials.gov with the accession number: NCT05646186. All authors had access to the study data and reviewed and approved the final manuscript. The study's main outcome measures include changes in the following parameters after 6 weeks of dietary intervention: IBS Symptom Severity Score (IBS-SSS), IBS QOL Scale (IBS-QOL), and Hospital Anxiety and Depression Scale (HADS).

Patient involvement

Patients actively participated in the design and implementation of this research. In the feasibility stage, discussions on recruitment methods and potential enhancements in patient participation primarily involved participants from the pilot clinical trial, offering invaluable insights from their firsthand experience with the personalized dietary approach. Following the publication of the trial, participants will receive comprehensive information about the outcomes through a study newsletter crafted for a non-specialist audience.

Randomization and masking

Patients who fulfilled the specified inclusion criteria were allocated randomly in a 1:1 ratio to either the PD or low-FODMAP diet group. The randomization process was performed in blocks of 5, using a computer-generated random number table procedure by staff members who were not involved in the treatment. The randomization sequences containing treatment assignments were pregenerated and placed inside opaque envelopes, maintaining confidentiality and blinding researchers to the content. Each envelope was individually sealed to prevent any interference. Subsequently, the research dietitians opened the envelopes before patient appointments, ensuring a controlled and fair allocation of participants to different groups. This systematic approach aimed to minimize observer bias and maintain the integrity of the study, ultimately leading to more reliable and valid conclusions. All patients assigned to either group received a minimum 20-minute face-to-face or online dietary consultation with a research dietitian and a comprehensive 6-week menu plan tailored to their assigned intervention (PD or FODMAP diet). The patients themselves prepared all the prescribed food following the instructions provided by the dietitian. The dietitians responsible for the consultations possessed relevant certifications and had graduated from accredited universities. To ensure unbiased evaluation, the investigators were blinded to the randomization process, and the data analysts remained unaware of the treatment allocation for each group.

Microbial DNA extraction and 16S ribosomal RNA sequencing

Stool samples were collected from all participants both before and after the dietary intervention. To ensure sample integrity, all collected samples were immediately stored at −80 °C until further processing. DNA isolations were conducted simultaneously upon the completion of the sample collection process. The DNA extraction from the stool samples was performed using the Qiagen Power Soil DNA Extraction Kit (Qiagen, Hilden, Germany). The quantification of double-stranded DNA (dsDNA) was performed using the Qubit dsDNA HS Assay Kit and Qubit 2.0 Fluorimeter (Thermo Fisher Scientific, Waltham, MA). After dsDNA measurements, the extracted DNA samples were stored at −20 °C until they were required for subsequent analysis.

16S ribosomal RNA sequencing was performed on an Illumina MiSeq system (Illumina, San Diego, CA) following the manufacturer's protocol for "16S Metagenomic Sequencing Library Preparation: Preparing 16S Ribosomal RNA Gene Amplicons for the Illumina MiSeq System." To create the sequencing library, the V4 hypervariable regions were amplified using the primer set 515F (5′—GTGCCAGCMGCCGCGGTAA- 3′) and 816R (5′ GGACTACHVGGGTWTCTAAT-3′) (18,19). For the final sequencing library preparation, a 15% PhiX Control (v3) (Illumina, San Diego, CA) was introduced into the library. The libraries were then subjected to cluster generation and underwent sequencing on 250 PE MiSeq runs, generating a minimum of 50,000 reads per sample.

Bioinformatic analysis

The QIIME2 pipeline (20) was used to analyze the sequencing data, following a filtration and trimming process of the reads using the Trimmomatic tool (21,22) for a PHRED quality score of 30. The Divisive Amplicon Denoising Algorithm 2 (DADA2) method facilitated the detection of amplicon sequence variants. Furthermore, the amplicon sequence variant representative sequences were classified into taxonomic clades using the Naive Bayesian Classifier, which was trained on the Silva database (version 132) (22). Alpha and beta diversities were evaluated using scikit-bio library (version 0.5.5) (23), and paired hypothesis testing was performed using 2-sided paired *t* test while Mann-Whitney *U*-test was used for independent comparisons. False discovery rate correction on *P* values was performed by using the Benjamini-Hochberg procedure. To visualize beta-diversity ordinations, multidimensional scaling to 2 coordinates on Bray-Curtis distances was used. The computations were performed using scikit-learn (version 0.23.1) (24) and scipy (version 1.4.1) (25) Python libraries.

The AI-based personalized nutrition model

The Enbiosis personalized nutrition model (ENBIOSIS Biotechnologies, London, UK), which is based on machine learning models to evaluate the microbiome and recommend conditioned nutritional actions (14), is used to determine the ideal micronutrient

compositions for modulating the microbiome. In this study, the model calculated the required microbiome modulation for an individual by analyzing the IBS indices generated by machine learning models. The baseline microbiome compositions were randomly perturbed with a small probability (P), and the perturbed profiles were accepted based on the decrease in the IBS index, following the principles of the Metropolis algorithm (26). This process involved a Monte-Carlo random walk in the microbiome composition space, aiming to find a nearby microbiome composition with a low IBS index similar to the patient's baseline composition, with minimal modulation. Subsequently, the personalized nutrition model estimated the optimized nutritional composition necessary to reduce the IBS index. The algorithm recommended daily diets based on the nutritional compositions suggested by the model. Thus, the algorithm evaluated the IBS index score using the microbiome composition to design optimized diets that aim to modulate the microbiome toward healthier scores.

Dietary interventions

The individualized food scoring for PD diet intervention was delivered by the same AI algorithm as described previously by Karakan et al (14). To evaluate the relationship between food and the microbiota, we established a comprehensive nutrient database encompassing various categories, such as carbohydrates, proteins, lipids, vitamins/minerals, phytochemicals, food additives, specific food items, and fermented foods. This involved conducting a meta-analysis to identify micronutrients associated with the growth or inhibition of specific microorganisms, based on *in vivo* studies. The final database includes these micronutrients and their corresponding target microorganisms. The database comprises a graph that identifies the set of micronutrients influencing specific microorganisms, either increasing or decreasing their relative abundance. When modulation of a particular subset of microorganisms is needed, the micronutrients affecting that subset are determined based on these interactions.

When striving for a preferred microbiome modulation, which typically aims to promote a healthier state with a focus on probiotic composition, relevant micronutrients are scored accordingly. It is important to note that a single micronutrient can target multiple microorganisms, and conversely, a single microorganism can be influenced by multiple micronutrients. This leads to varying preferences for certain micronutrients and, as a result, a broad range of differential scores, all graded on a relative scale from 0 to 10.

The FODMAP diet involved a restricted intake of foods containing fermentable oligosaccharides, monosaccharides, disaccharides, and polyols (27). Patients randomly assigned to follow this diet were provided with a pamphlet containing detailed information about the foods to avoid and alternative options that could be safely consumed. The written resources used in developing these guidelines were based on previously published materials from the American College of Gastroenterology (28). It involves avoiding foods rich in fermentable carbohydrates, particularly fructans and galacto-oligosaccharides, found in wheat, rye, barley, onion, and legumes. Lactose-containing products, such as milk and dairy items, are also excluded, as are foods high in free fructose, such as apples, pears, watermelon, asparagus, and honey. In addition, foods containing sugar alcohols such as sorbitol, mannitol, maltitol, and xylitol, such as apricots, peaches, and artificially sweetened products, are discouraged.

The PD was planned with the foods recommended by AI according to the results of the microbiome analysis (14). Approximately 300 foods were scored between 0 and 10 for microbiome modulation. Foods with a score of 0–3 were defined as foods that should be avoided, foods with a score of 4–7 were defined as foods that should be diversified in the diet, and foods with a score of 8–10 were defined as foods needed. The dietitian mainly planned the diet with foods with a score of 4–10. High-scoring fruits were added to the diet lists. Low-scoring foods were not recommended in this process. Raw greens and legumes were restricted in the first weeks, and then high-scoring foods were included in the diet. The dissimilarity in dietary content between the 2 diets was evaluated using the Jaccard index. This index offers a quantitative assessment of dietary overlap, encompassing both shared and distinct food recommendations (29).

Patient monitoring

The symptom severity of the patients with IBS was assessed using the IBS-SSS at the beginning and end of the study. The IBS-SSS is a validated questionnaire that measures the severity of IBS symptoms, including abdominal pain, bloating, stool frequency, and stool consistency. Higher scores on the IBS-SSS indicate more severe symptoms. The IBS-SSS total score can range from 0 to 500, and IBS symptom severity is classified as mild: 75 to 175, moderate: 175 to 300, and severe: >300 (30).

The patients recorded all bowel movements in a stool diary (Bristol Stool Scale) every day during the intervention period of 6 weeks (31).

At the beginning and end of the study, the QOL of patients was assessed using the IBS-QOL. The IBS-QOL is a validated questionnaire that measures how IBS affects various aspects of a person's life, including physical, emotional, and social well-being (32).

At the beginning and end of the study, the participants were administered the HADS. The HADS is a widely used self-assessment questionnaire to detect anxiety and depression in individuals, particularly in medical settings. It consists of 2 subscales, one for anxiety and the other for depression. Each subscale contains 7 items, and respondents rate each item based on their feelings over the past week. The total scores for anxiety and depression can range from 0 to 21, with higher scores indicating a higher level of anxiety or depression (33).

Dietary adherence assessment

Dietary adherence was evaluated through self-rated dietary compliance during weekly phone calls. Participants were asked to assess their adherence to the prescribed diet over the past week, using the following response options: never/rarely (<25% of the time), sometimes (25%–50% of the time), frequently (51%–75% of the time), and always (76%–100% of the time). In the weekly assessments, participants were considered compliant if they reported following the diet frequently or always in at least 3 of the 6 evaluations. This criterion ensured that patients who consistently adhered to the diet were classified as compliant.

Statistical analysis

Statistical analysis was performed using SPSS version 21 (IBM, Armonk, NY). Descriptive statistics were used to summarize the demographic characteristics of the participants, including means, SDs, frequencies, and percentages as appropriate. Continuous variables were expressed as means ± SDs while categorical

variables were presented as frequencies and percentages. To assess the effectiveness of the diet intervention, paired t-tests or Wilcoxon signed-rank tests were used to compare pre and postintervention measurements, depending on the distributional assumptions of the data. The significance level was set at $P < 0.05$. The actual P values were log-transformed for representation purposes. Cohen d metric was used to assess the effect size comparisons of both interventions (34). The study's sample size determination involved a power calculation based on an effect size of 0.8 (Cohen d), aiming for 80% power at a significance level (α) of 0.05 with an assumed SD of 100.

Furthermore, subgroup analyses were conducted to explore potential differences in treatment response based on specific demographic or clinical variables. χ^2 tests or independent t tests were used to compare categorical or continuous variables between subgroups, respectively. In addition, correlation analyses, such as Pearson correlation coefficient or Spearman rank correlation coefficient, were performed to examine the relationship between variables of interest. Permutational multivariate analysis of variance (PERMANOVA) was used to assess differences between groups in multivariate data sets, considering potential differences beyond those captured by univariate methods. All statistical tests were 2-tailed, and a P value less than 0.05 was considered statistically significant. The results were presented using appropriate tables and figures to enhance clarity and facilitate data interpretation.

RESULTS

Baseline characteristics of patients

The power analysis determined a minimum sample size of 25 patients per group. Initially, 149 patients were randomized, with 75 assigned to the PD group and 74 to the FODMAP diet group. Subsequently, 28 patients withdrew from the study for diverse reasons. Consequently, the final cohort comprised 121 patients,

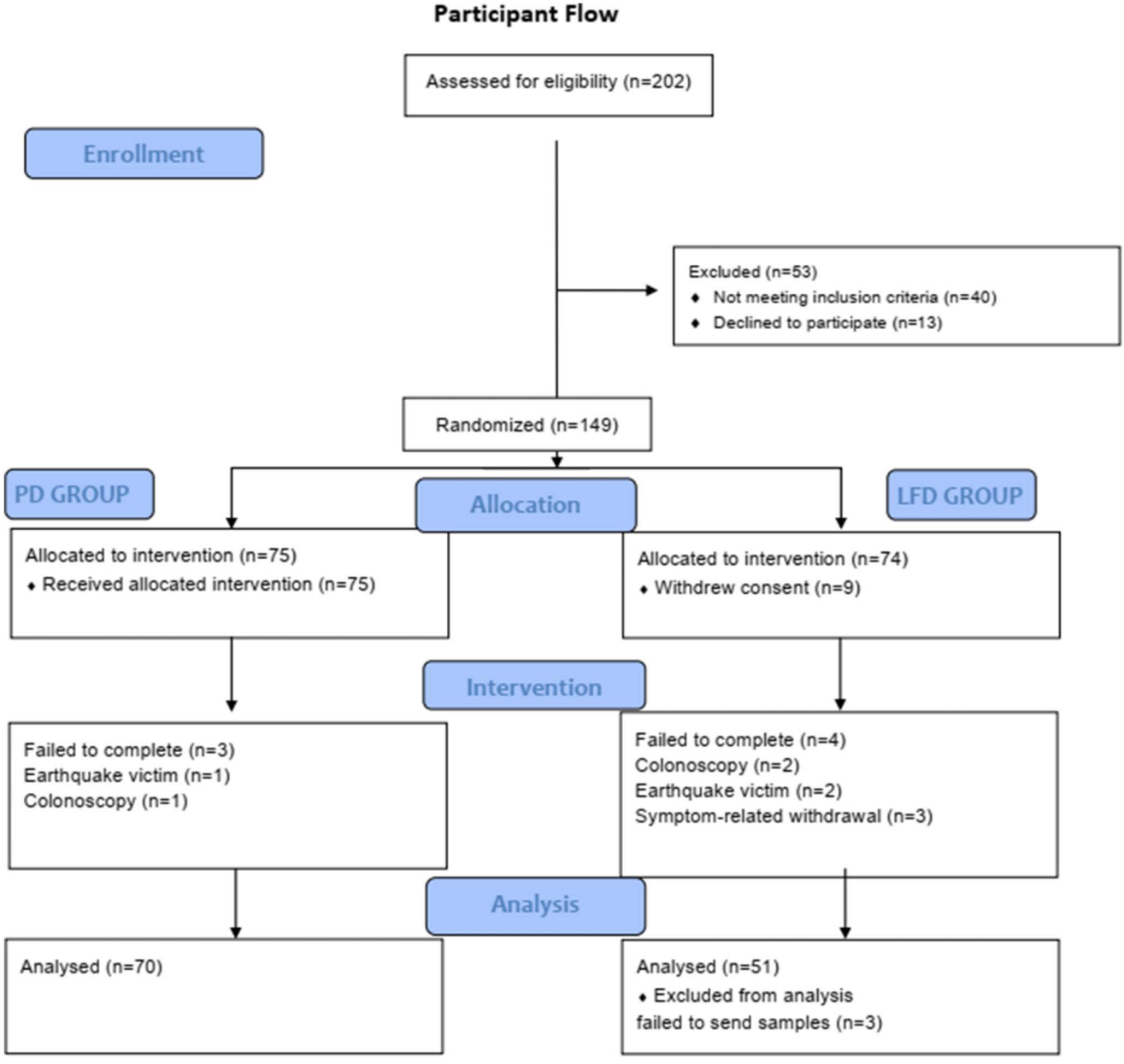

Figure 1. CONSORT diagram.

Table 1. Baseline characteristics of patients

	PD group (n = 70)	FODMAP diet group (n =51)	*P* value
Age	35.94 ± 10.13	37.9 ± 9.87	0.71
Sex (female)	42 (60)	31 (60.8)	0.25
IBS-C	32 (45.7)	24 (46.4)	0.82
IBS-M	22 (31.4)	17 (32.8)	0.79
IBS-D	16 (22.9)	10 (19.24)	0.78
IBS-SSS	314.41 ± 92.79	276.76 ± 90.15	0.59
Mild	5 (7.14)	5 (9.8)	0.84
Moderate	30 (42.86)	24 (47.1)	0.49
Severe	35 (50.0)	22 (43.1)	0.59
Stool frequency	7.13 ± 4.81	5.09 ± 2.17	0.54
Stool consistency	3.43 ± 1.40	3.81 ± 1.06	0.37
HADS (anxiety)	10.27 ± 4.22	10.75 ± 3.96	0.82
HADS (depression)	10.75 ± 3.96	8.33 ± 4.36	0.77
IBS-QOL score	45.55 ± 22.06	42.65 ± 19.82	0.83

HADS, Hospital Anxiety and Depression Scale; IBS-C, IBS-Constipation; IBS-D, IBS-Diarrhea; IBS-M, IBS-Mixed; IBS-QOL, IBS Quality of Life; IBS-SSS, Irritable Bowel Syndrome Severity Scoring System.

with 70 in the PD group and 51 in the FODMAP diet group (Figure 1). Among the patients, the majority were female, with 60% in both the PD and FODMAP diet groups ($P = 0.25$) (Table 1). In terms of demographic profiles, no statistically significant difference was observed between the PD and FODMAP groups.

IBS subtypes were determined based on the Bristol Stool Scale and defecation frequency (35), and the most common subtype in both groups was IBS-Constipation (IBS-C), accounting for 45.7% in the PD group and 46.4% in the FODMAP diet group ($P = 0.82$). The next most prevalent subtype was IBS-Mixed (IBS-M), with 31.4% in the PD group and 32.8% in the FODMAP diet group ($P = 0.79$), followed by IBS-Diarrhea (IBS-D), with 22.9% in the PD group and 19.24% in the FODMAP diet group ($P = 0.78$).

Postintervention results

Overall symptom assessment of the groups. Table 2 presents an overall comparison of symptom-based parameters between the PD group (n = 70) and the FODMAP diet group (n = 51) after 6 weeks of intervention. The difference in the *P* values of the conducted tests for both groups was shown in terms of negative log-transformed ratios. The primary outcomes revealed significant changes in various parameters. The change in IBS-SSS was observed as −112.7 in the PD group compared with −99.9 in the FODMAP diet group (*P*: 0.29) (Figure 2). In terms of IBS-QOL, the PD group showed a change of 10.24, whereas the FODMAP diet group demonstrated a change of 12.43. In addition, for HADS scores, the PD group exhibited changes in anxiety and depression of 2.12 and 1.35 while the FODMAP diet group showed changes of 2.88 and 2.61, respectively (Table 2) (Figure 3).

Both groups showed significant improvements in abdominal pain severity ($P < 0.001$) and frequency ($P < 0.001$), as well as abdominal distension severity ($P < 0.001$) and bowel habits dissatisfaction ($P < 0.001$). Life interference due to IBS symptoms significantly decreased in both groups ($P < 0.001$).

IBS-SSS scores according to IBS subtypes. The baseline and 6-week IBS-SSS scores for different IBS subtypes, namely IBS-C, IBS-D, and IBS-M, in the PD and FODMAP diet groups are summarized in Table 3. The IBS-SSS scores significantly improved from baseline to 6 weeks in all subtypes and both dietary intervention groups (PD and FODMAP diet). In the IBS-C subtype, both PD and FODMAP diet interventions resulted in a significant reduction in IBS-SSS scores ($P < 0.001$). Similarly, for the IBS-D subtype, the PD intervention led to a more pronounced decrease in IBS-SSS scores ($P = 0.010$), compared with the FODMAP diet ($P = 0.312$). In the IBS-M subtype, both PD and FODMAP diet interventions were associated with a significant improvement in IBS-SSS scores ($P < 0.001$).

IBS-QOL scores according to IBS subtypes. The baseline and 6-week IBS-QOL scores for different IBS subtypes in the PD and FODMAP diet groups are summarized in Table 3. At 6 weeks, the PD intervention demonstrated a significant improvement in IBS-QOL scores compared with the baseline for IBS-C ($P < 0.001$), IBS-D ($P < 0.001$), and IBS-M ($P = 0.008$) subtypes. By contrast, the FODMAP diet intervention showed a significant improvement in IBS-QOL scores only for the IBS-C ($P = 0.004$) and IBS-D ($P = 0.022$) subtypes while no significant changes were observed for the IBS-M ($P = 0.646$) subtype.

These findings suggest that the PD intervention resulted in significant improvements in IBS-QOL scores across multiple IBS subtypes, indicating a positive impact on the overall QOL of individuals with IBS.

Dietary adherence and microbiome changes. The Jaccard similarity index, serving as a numerical representation of the dietary overlap between PD and FODMAP diet, yielded a value of 0.29. This result indicates a moderate level of similarity between the 2 diets. Before obtaining the Jaccard similarity index, a detailed examination was conducted on the high-scored and most frequently recommended foods by AI in PD-applied individuals. These findings were then contrasted with the recommendations in the FODMAP diet group.

Table 4 (see Supplementary Material, http://links.lww.com/AJG/D284) provides a summary of dietary compliance in the PD and FODMAP diet groups. The table presents the percentage of participants who reported different levels of compliance with their respective diets. Most of the participants in both groups reported high levels of compliance with their respective diets, with the PD group showing slightly higher levels of compliance compared with the FODMAP diet group.

The dietary adherence rates of patients whose IBS-SSS scores did not improve after the intervention are provided in Table 5 (see Supplementary Material, http://links.lww.com/AJG/D284). Among patients in the PD group whose IBS-SSS scores did not show improvement, a notable percentage reported occasional compliance with the prescribed diet. Conversely, in the FODMAP diet group, there was a significantly higher proportion of patients consistently adhering to the dietary regimen, despite non-improvement in IBS-SSS scores.

Diversity shifts. After 6 weeks of intervention, significant shifts were observed in alpha diversities in the PD group, but no such change was visible in the FODMAP diet group (Table 6, see Supplementary Material, http://links.lww.com/AJG/D284). The increase in Shannon diversity was more significant for IBS-C and IBS-D cases while IBS-M cases did not exhibit a statistically significant change in the PD group (Figure 4).

Table 2. Comparison of gastrointestinal symptom scores, bowel habits, hospital anxiety and depression scores, and quality of life in both groups

	PD group (n = 70)			FODMAP diet group (n = 51)				
	Baseline	6 wk	Within-group change *P* value	Baseline	6 wk	Within-group change *P* value	Effect size (Cohen *d*)	Difference in reduction across groups, *P* value
Pain abdomen—severity	51.90 ± 32.84	26.98 ± 29.98	<0.001	47.06 ± 28.14	20.65 ± 28.96	<0.001	0.41	0.41
Pain abdomen—frequency	40.43 ± 30.52	27.28 ± 32.21	<0.001	44.71 ± 27.59	20.29 ± 28.95	<0.001	0.38	0.37
Abdominal distension—severity	72.62 ± 22.82	40.66 ± 34.76	<0.001	57.94 ± 28.38	31.75 ± 36.05	<0.001	0.15	0.44
Bowel habits dissatisfaction	74.02 ± 30.79	50.38 ± 32.20	<0.001	61.25 ± 25.65	42.86 ± 28.90	<0.001	0.14	0.47
Life interference in general	82.17 ± 21.48	56.2 ± 36.06	<0.001	70.04 ± 26.94	56.02 ± 34.14	0.02	0.39	0.97
Total IBS-SSS	314.42 ± 92.79	210.64 ± 130.63	<0.001	276.76 ± 90.15	176.86 ± 111.09	<0.001	0.11	0.29
Stool frequency per d	7.13 ± 4.81	7.02 ± 2.87	.70	5.09 ± 2.17	5.41 ± 1.59	0.11	0.21	0.87
BSFS score	3.43 ± 1.40	3.70 ± 0.73	0.02	3.65 ± 1.45	3.81 ± 1.06	0.24	0.11	0.49
IBS-QOL score	45.55 ± 22.06	55.79 ± 21.85	<0.001	42.65 ± 19.82	55.08 ± 23.62	<0.001	0.11	0.97
HADS (anxiety)	10.27 ± 4.22	8.15 ± 3.37	<0.001	10.74 ± 3.95	7.86 ± 4.07	<0.001	0.16	0.87
HADS (depression)	7.57 ± 4.35	6.22 ± 4.10	0.02	8.33 ± 4.36	5.72 ± 4.35	<0.001	0.25	0.93

BSFS, Bristol Stool Form Scale; IBS-QOL, Irritable Bowel Syndrome Quality of Life; IBS-SSS, Irritable Bowel Syndrome Severity Scoring System; HADS, Hospital Anxiety and Depression Scale; PD, personalized diet; FODMAP diet, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet.

The initial beta diversities in the baseline (i.e., the pre-intervention subgroups) were not significantly different between the PD and low-FODMAP intervention groups ($P = .996$ for IBS-C, 0.457 for IBS-D, and $P = 0.06$ for IBS-M). Therefore, it can be claimed that more significant alterations were observed on average in the PD group.

Alterations in specific taxa relative abundances. A significant increase in the abundance of *Faecalibacterium prausnitzii* was observed in the PD group ($P < 10^{-4}$, paired *t* test), whereas no such change was observed in the low-FODMAP group ($P > 0.05$) (Figure 5). A similar trend was observed in the decrease of the Ruminococcaceae family for the PD group ($P < 10^{-5}$) while no

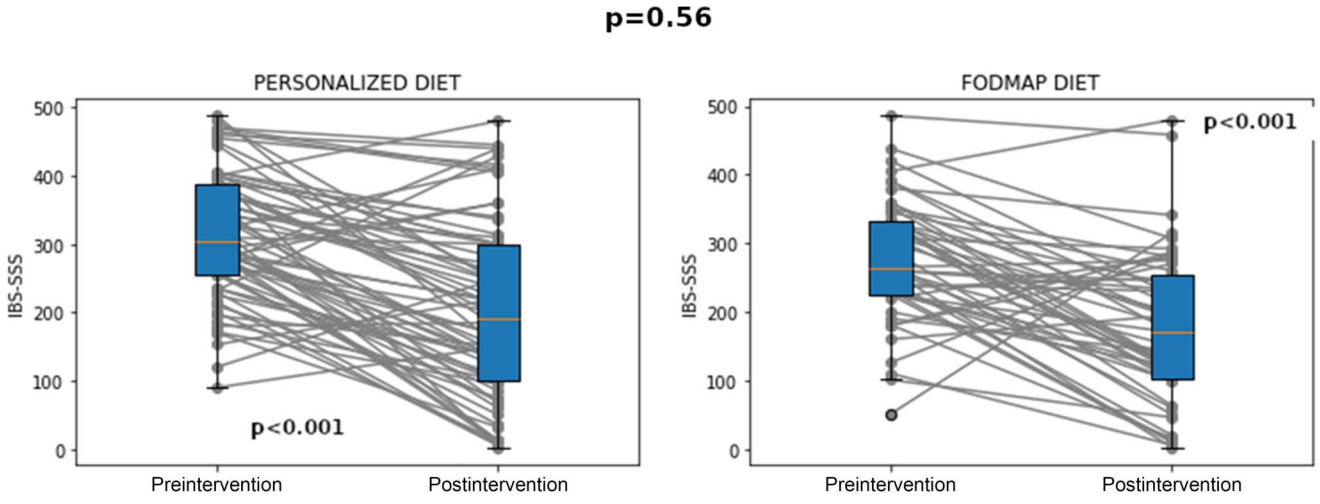

Figure 2. Box-and-whisker plot of total IBS-SSS scores before and after intervention for both groups. The *P* values within the groups are reported based on paired *t* tests. The *P* value for the comparison of score differences between 2 groups is shown at the top of the figure (independent *t* test). IBS-SSS, Irritable Bowel Syndrome Severity Scoring System.

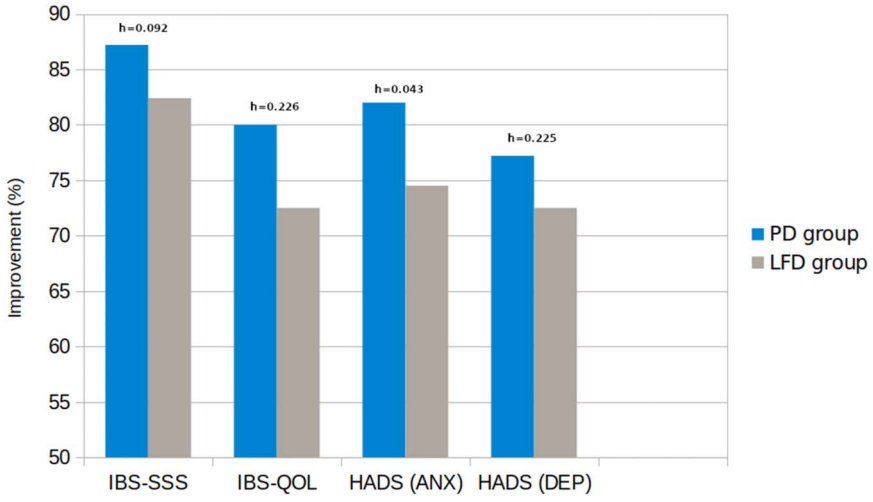

Figure 3. Percentage improvement for specific scoring indices. The effect size of the improvements between the 2 interventions was calculated by Cohen effect size and reported as (h). IBS-SSS, Irritable Bowel Syndrome Severity Scoring System; IBS-QOL, IBS Quality of Life; HADS-ANX, Hospital Anxiety and Depression Scale-Anxiety; HADS-DEP, Hospital Anxiety and Depression Scale-Depression.

significant change was apparent in the low-FODMAP group ($P > 0.05$) (Figure 5).

DISCUSSION

This study aimed to investigate the effects of 2 dietary interventions, namely the microbiome-based AI-assisted PD and the FODMAP diet, on individuals with IBS across different subtypes, as classified by the Rome IV criteria. Our findings contribute to a comprehensive understanding of the potential benefits of personalized dietary interventions tailored to specific IBS subtypes.

The PD intervention demonstrated significant improvements in IBS-SSS and IBS-QOL across various IBS subtypes. Notably, it showed a substantial effect in alleviating symptoms in the IBS-D subtype, with a large effect size (Cohen $d = 0.81$). These results align with previous studies highlighting the efficacy of personalized dietary approaches for IBS symptom relief in patients with different subtypes (36,37). On the other hand, the FODMAP diet intervention showed significant improvements in IBS-SSS scores for the IBS-C and IBS-M subtypes.

Regarding the overall IBS-QOL outcomes, the PD intervention led to significant improvements for all subtypes while the FODMAP diet intervention showed significant improvements only for the IBS-C and IBS-D subtypes. These findings support the potential of a personalized dietary approach to not only alleviate symptoms but also enhance the overall QOL for individuals with IBS.

As a comparative trial by design, our study intentionally lacked a placebo or no-treatment arm, with the FODMAP diet serving as the comparator (38). Several studies have established the effectiveness of

Table 3. IBS-SSS and IBS-QOL scores stratified by IBS subtypes

	IBS-SSS			
	Baseline	**6 wk**	***P* value**	**Effect size (Cohen *d*)**
IBS-C PD	327.91 ± 97.74	201.68 ± 122.67	<0.001	0.07
IBS-C FODMAP diet	295.46 ± 85.94	192.75 ± 119.45	<0.001	
IBS-D PD	306.06 ± 100.88	221.13 ± 126.24	0.010	0.81
IBS-D FODMAP diet	223.08 ± 97.44	170.75 ± 109.81	0.312	
IBS-M PD	300.86 ± 80.01	187.41 ± 148.24	<0.001	0.14
IBS-M FODMAP diet	290.71 ± 74.47	157.82 ± 101.91	<0.001	
	IBS-QOL			
	Baseline	**6 wk**	***P* value**	**Effect size (Cohen *d*)**
IBS-C PD	45.86 ± 22.25	55.30 ± 22.90	<0.001	0.40
IBS-C FODMAP diet	41.36 ± 17.52	58.35 ± 23.75	0.04	
IBS-D PD	45.82 ± 25.21	58.41 ± 20.83	<0.01	0.08
IBS-D FODMAP diet	41.67 ± 20.90	60.25 ± 22.74	0.22	
IBS-M PD	44.89 ± 20.35	54.60 ± 21.85	0.08	0.18
IBS-M FODMAP diet	45.93 ± 21.96	48.21 ± 22.55	0.646	

IBS-C, IBS-Constipation; IBS-D, IBS-Diarrhea; IBS-M, IBS-Mixed; IBS-QOL, Irritable Bowel Syndrome Quality of Life; IBS-SSS, Irritable Bowel Syndrome Severity Scoring System; FODMAP diet, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet; PD, personalized diet.

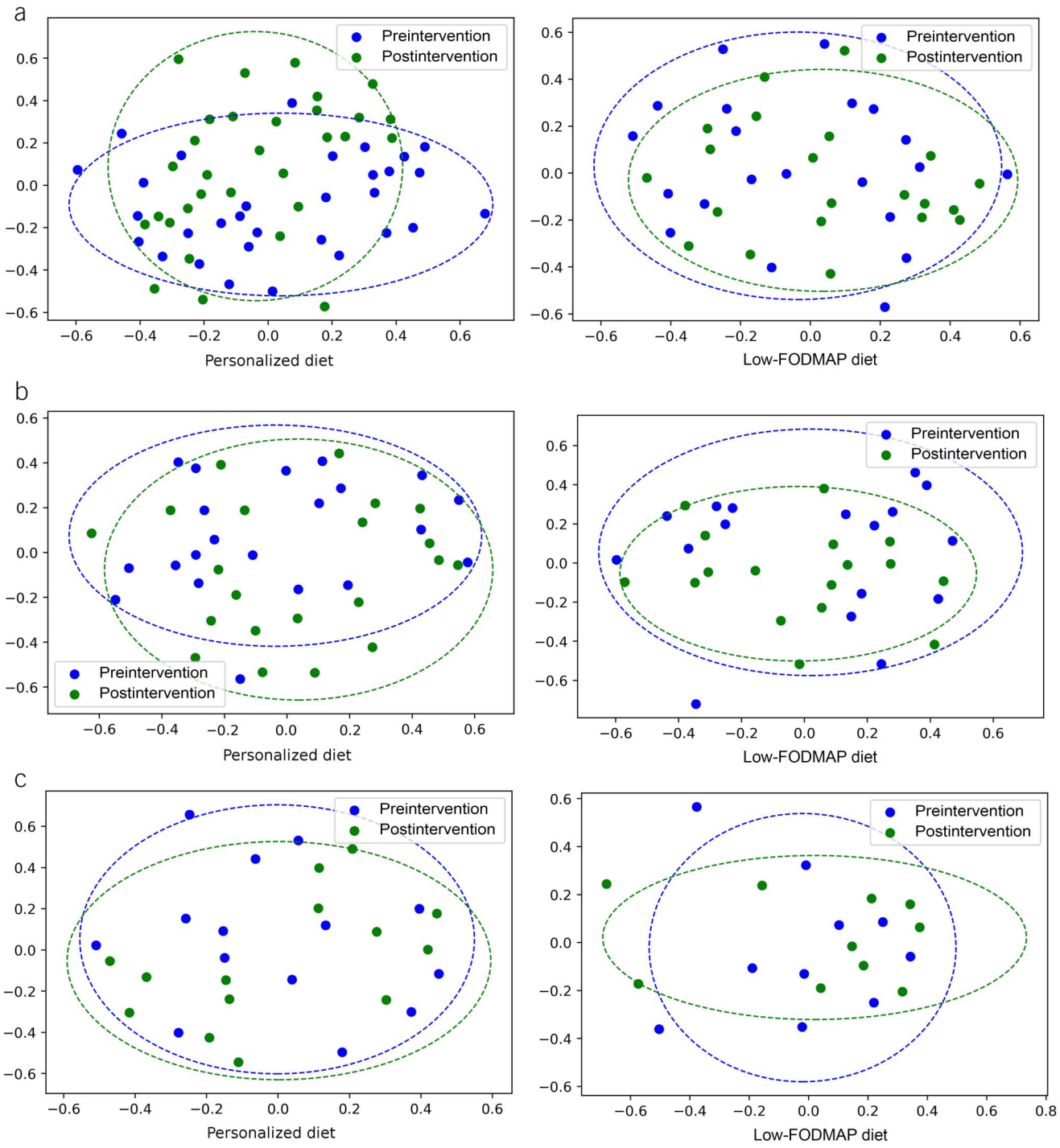

Figure 4. Pre and postintervention ordination in microbial Bray-Curtis diversity for the subgroups. (**a**) IBS-C, (**b**) IBS-D, (**c**) IBS-M groups. The *P* values are reported using the PERMANOVA test with 99,999 random permutations. IBS-C, IBS-Constipation; IBS-D, IBS-Diarrhea; IBS-M, IBS-Mixed.

the FODMAP diet in reducing symptoms and improving the QOL in patients with IBS, and it is one of the standard-of-care diets in IBS management (39–41). Nonetheless, our results highlight the potential benefits of personalized dietary interventions tailored to specific IBS subtypes. In addition, our study is the first randomized controlled trial to assess a microbiome-based PD with an active comparator: a FODMAP diet. Our goal was to compare the PD with prevailing standard dietary advice (FODMAP diet) (42).

Tailoring dietary interventions to specific IBS subtypes seems to be a promising strategy for optimizing treatment outcomes. The observed differential responses underscore the importance of considering the underlying pathophysiology and symptom patterns associated with each IBS subtype when designing dietary interventions (42). By incorporating individualized dietary recommendations based on patients' symptom profiles and gut microbiome composition, a personalized approach can potentially

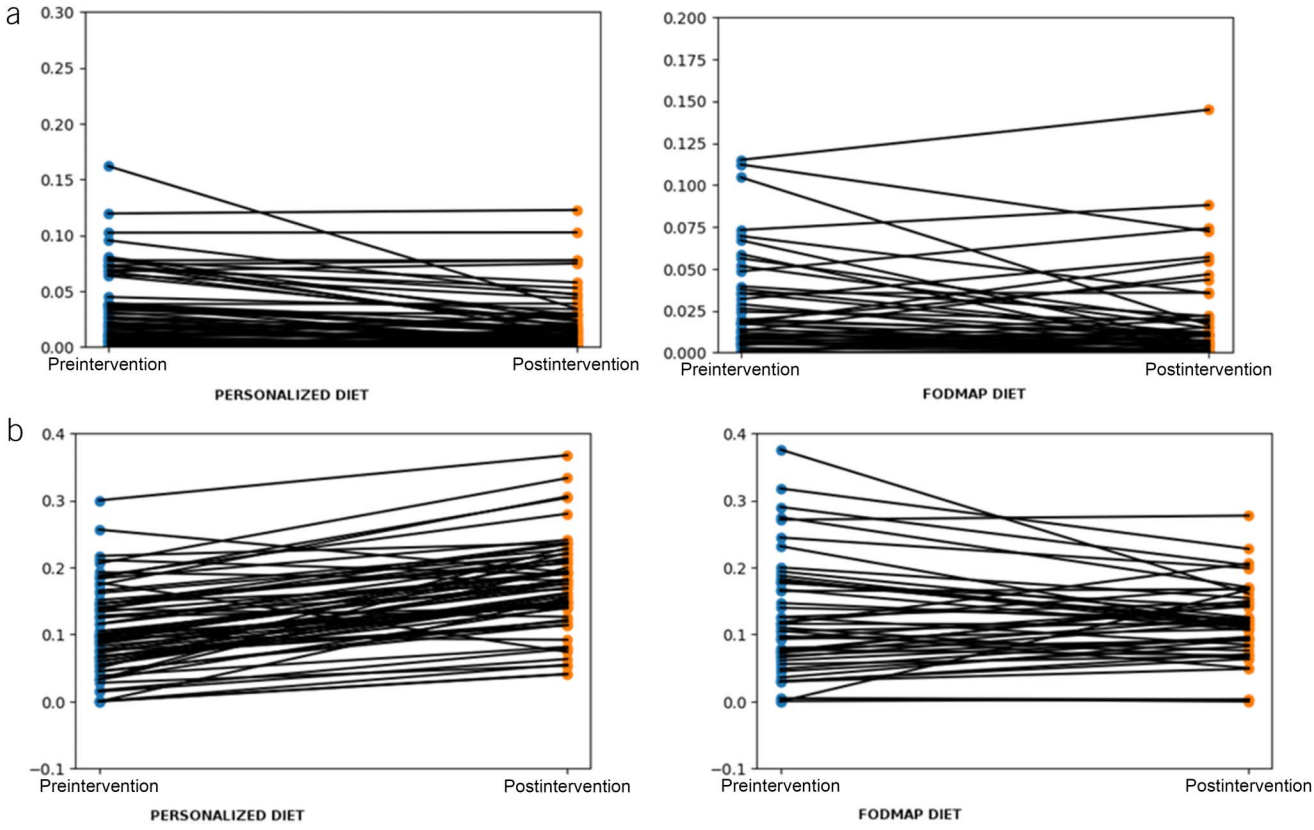

Figure 5. Pre and postintervention change in relative abundance for (**a**) the Ruminococcaceae family and (**b**) *Faecalibacterium prausnitzii*.

target the unique mechanisms contributing to symptom generation and provide more targeted symptom relief (43,44).

While our study primarily focused on evaluating the effects of dietary interventions on symptoms and QOL, it is important to note that we additionally explored the mechanistic links between the interventions and changes in the gut microbiome. As previous research has established associations between gut microbiome alterations and IBS symptoms (10,43), our study observed positive influences of the PD intervention on gut microbiome profiles, including increased alpha and beta diversities and the abundance of beneficial bacteria like *F. prausnitzii*. Conversely, the FODMAP diet intervention did not exhibit similar positive effects on gut microbiome parameters, especially in means of alpha diversity. These observations suggest that the PD intervention may have a broader impact on gut health, potentially contributing to its effectiveness in improving symptoms and QOL in patients with IBS.

Multiple studies have reported increased levels of Ruminococcus species in individuals with IBS compared with healthy controls (45,46). Interestingly, it has been found that nonresponders to the FODMAP diet exhibited even higher levels of *Ruminococcus* (47). This suggests the potential significance of the Ruminococcaceae family in IBS management and indicates that a PD approach may be more effective for individuals who do not respond well to the FODMAP diet. However, within this family, a specific species called *F. prausnitzii* showed an inverse response, increasing in abundance after PD intervention. This particular species is notable for its anti-inflammatory properties and its ability to produce short-chain fatty acids, especially butyrate, which nourishes the gut lining cells and reduces inflammation (48). Previous studies have reported a reduced abundance of *F. prausnitzii* in individuals with IBS compared with healthy controls (49), suggesting that increasing the abundance of this species may have beneficial outcomes for IBS management. Although *F. prausnitzii* is not currently available as a probiotic for dietary supplementation, it may be possible to promote the growth of existing members of the gut ecosystem through nutrition, and a PD approach could be a potential strategy to achieve this.

The alterations in the beta diversity of gut microbiota in IBS seem to be influenced by various factors, including the subtype of IBS. It was noted that different IBS subtypes (IBS-D, IBS-C, and IBS-M) had different gut microbiota compositions (11). Regarding beta-diversity changes, both interventions resulted in statistically significant shifts for IBS-C and IBS-M cases (PERMANOVA test, $P < 0.05$), with the PD showing more emphasized shifts and lower P values. However, the changes in the IBS-D group did not result in statistically significant diversity shifts.

Our study also aimed to evaluate the efficacy of a microbiome-based AI-assisted PD in IBS management, representing the first multicenter randomized controlled trial focusing on this approach. By prioritizing microbiome diversity and health, we aimed to provide a more comprehensive and targeted therapeutic strategy for individuals with IBS, potentially yielding long-term benefits beyond symptom relief (50,51). A limitation of our study is the uneven distribution of participants between the groups, with a larger number of patients in the PD group compared with the FODMAP diet group. This difference in sample size may have affected the statistical power, potentially leading to an enhanced ability to detect differences in outcomes between the groups. Moreover, during the study, 28 participants dropped out for various reasons, resulting in a completion rate of 81%. Although

there was a significant difference in drop-out rates between the intervention and comparator arms, no systematic differences in drop-out reasons were observed between the 2 groups. To assess potential bias due to attrition, we compared the baseline characteristics of participants who completed the study between the 2 groups, revealing no statistically significant differences in demographic and clinical characteristics at baseline. Random attrition occurred during the study, and despite efforts to retain participants, the drop-out rates remained within an acceptable range. In addition, the assessment of the genetic and metabolic parameters of each individual was not conducted. We hold the perspective that an integrated approach taking into account these factors would likely produce more favorable outcomes concerning the alleviation of IBS symptoms. To tackle this challenge, we are actively engaged in developing collaborative study designs. Furthermore, while a duration of 6 weeks for dietary intervention aligns with prevalent practices in the existing literature, it is worth considering that extended dietary modifications could potentially render distinct outcomes with regard to microbiome modulation and symptomatic effects. Thus, it is recommended that forthcoming research endeavors concentrate on the comparative analysis of varying durations of dietary interventions, accompanied by the comprehensive long-term monitoring of patients both during and following the intervention phases.

In conclusion, our study provides evidence supporting the effectiveness of a tailor-made PD, such as the PD, for managing IBS symptoms and improving QOL across different subtypes. While the FODMAP diet remains the standard dietary approach for symptom relief in many clinical settings, our findings suggest that considering individual patient characteristics, including the IBS subtype, may further optimize treatment outcomes and by achieving a healthier microbiome status, the overall health status of patients with IBS may be improved. Future research should continue to explore the underlying mechanisms and long-term effects of personalized dietary interventions on gut microbiome composition, symptom relief, and overall well-being in patients with IBS. In addition, investigating potential biomarkers or patient characteristics that may predict differential responses to specific dietary interventions could help refine and personalize treatment strategies for IBS. This trial is registered on ClinicalTrials.gov with the accession number: NCT05646186.

CONFLICTS OF INTEREST

Guarantor of the article: Varol Tunali, MD, PhD.

Specific author contributions: V.T., N.C.A.: conceptualization. V.T., B.H.E.: data curation. Ö.U.N., B.H.E., A.G.: formal Analysis. V.T., Ö.U.N.: funding acquisition. V.T., N.C.A., G.D.H., Ö.U.N.: investigation. V.T., N.C.A., Ö.U.N.: methodology. V.T.: project administration. B.H.E., M.H., A.G.: software. Ö.U.N., M.H.: resources. V.T., Ö.U.N., A.G.: supervision. V.T., G.D.H., B.H.E.: validation. V.T., Ö.U.N.: visualization. V.T., B.H.E., Ö.U.N., A.G.: writing–original Draft. V.T., Ö.U.N., N.C.A., G.D.H., A.G.: writing–review & editing.

Financial support: This research received no external funding, but the microbiome analysis was carried out by ENBIOSIS Biotechnology. A. Gündoğdu and Ö.U. Nalbantoğlu are shareholders of ENBIOSIS Biotechnologies.

Potential competing interests: Beyza Hilal Ermis and Mehmet Hora are scientists working with ENBIOSIS Biotechnologies.

Data transparency statement: Deidentified individual participant data that underlie the reported results will be made available 3 months after publication for 5 years after the publication date at https://data.mendeley.com/. The study protocol is included as a data supplement available with the online version of this article.

Study Highlights

WHAT IS KNOWN

- ✓ Personalized management strategies are crucial in addressing irritable bowel syndrome (IBS).
- ✓ The efficacy of low-FODMAP diets for IBS management has been investigated.

WHAT IS NEW HERE

- ✓ Microbiome-based artificial intelligence-assisted personalized diets (PDs) show promise for IBS management.
- ✓ PD demonstrates effectiveness in reducing symptoms of IBS across all subtypes.
- ✓ PD intervention leads to significant microbiome diversity shifts.

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