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CLINICAL AT

Effects of Low FODMAP Diet on Symptoms, Fecal Microbiome, and Markers of Inflammation in Patients With Quiescent Inflammatory Bowel Disease in a Randomized Trial

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BACKGROUND & AIMS: There is limited evidence that a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) reduces gut symptoms in quiescent inflammatory bowel disease (IBD). We performed a randomized, controlled trial to investigate the effects of a low FODMAP diet on persistent gut symptoms, the intestinal microbiome, and circulating markers of inflammation in patients with quiescent IBD. **METHODS:** We performed a single-blind trial of 52 patients with quiescent Crohn's disease or ulcerative colitis and persistent gut symptoms at 2 large gastroenterology clinics in the United Kingdom. Patients were randomly assigned to groups that followed a diet low in FODMAPs (n = 27) or a control diet (n = 25), with dietary advice, for 4 weeks. Gut symptoms and health-related quality of life were measured using validated questionnaires. Stool and blood samples were collected at baseline and end of trial. We assessed fecal microbiome composition and function using shotgun metagenomic sequencing and phenotypes of T cells in blood using flow cytometry. **RESULTS:** A higher proportion of patients reported adequate relief of gut symptoms following the low FODMAP diet (14/27, 52%) than the control diet (4/25, 16%, P=.007). Patients had a greater reduction in irritable bowel syndrome severity scores following the low FODMAP diet (mean reduction of 67; standard error, 78) than the control diet (mean reduction of 34; standard error, 50), although this difference was not statistically significant ($P = .075$). Following the low FODMAP diet, patients had higher health-related quality of life scores (81.9 ± 1.2) than patients on the control diet (78.3 ± 1.2, $P = .042$). A targeted analysis revealed that in stool samples collected at the end of the study period, patients on the low FODMAP diet had significantly lower abundance of *Bifidobacterium adolescentis*, *Bifidobacterium longum*, and *Faecalibacterium prausnitzii* than patients on control diet. However, microbiome diversity and markers of inflammation did not differ significantly between groups. **CONCLUSIONS:** In a trial of the low FODMAP diet vs a control diet in patients with quiescent IBD, we found no significant difference after 4 weeks in change in irritable bowel syndrome severity scores, but significant improvements in specific symptom scores and numbers reporting adequate symptom relief. The low FODMAP diet reduced fecal abundance of microbes believed to regulate the immune response, compared with the control diet, but had no significant effect on markers of inflammation. We conclude that a 4-week diet low in FODMAPs is safe and effective for managing persistent gut symptoms in patients with quiescent IBD. www.isrctn.com no.: ISRCTN17061468

Keywords: CD; UC; IBS; HR-QOL.

An estimated 35% of patients with inflammatory bowel disease (IBD) experience gut symptoms despite having quiescent disease with minimal objective evidence of gastrointestinal (GI) inflammation.[1] The etiology of these gut symptoms in quiescent IBD is unclear but they are hypothesized to relate to coexistent irritable bowel syndrome (IBS), the legacy of previous GI inflammation on gut function, persistent unidentified low-grade inflammation, or the psychological impact of IBD.[2] These persistent gut symptoms have a significant impact on health-related quality of life (HR-QOL)[3] and pose a treatment dilemma because escalating

Abbreviations used in this paper: **bp, base pair; CD, Crohn's disease; CRP, C-reactive protein; FDR, false discovery rate; FODMAPs, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols; GI, gastrointestinal; GOS, galacto-oligosaccharides; GSRS, GI symptom rating scale; HR-QOL, health-related quality of life; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IBS-SSS, IBS Severity Scoring System; IHMS, International Human Microbiome Standards; ITT, intention-to-treat; KEGG, Kyoto Encyclopedia of Genes and Genomes; MGS, metagenomic species; PP, per protocol; SCFA, short chain fatty acid; SD, standard deviation; SEM, standard error of the mean; UC, ulcerative colitis.**

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

We performed a randomized trial to investigate the effects of diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) on symptoms not accompanied by inflammation, the fecal microbiome, and circulating markers of inflammation in patients with quiescent inflammatory bowel disease (IBD).

NEW FINDINGS

In comparing outcomes of patients on the low FODMAP diet vs a control diet, we found no significant difference after 4 weeks on change in irritable bowel syndrome severity scores, but significant improvements in specific gut symptom scores and the numbers reporting adequate symptom relief. The low FODMAP diet reduced fecal abundance of microbes believed to regulate the immune response, compared with the control diet, but had no significant effect on markers of inflammation.

LIMITATIONS

This trial included only 52 patients, placed on the diet for 4 weeks. Larger, more long-term studies might be needed.

IMPACT

A 4-week diet low in FODMAPs is safe and effective for managing intestinal symptoms not associated with inflammation in patients with quiescent IBD.

immune-modulating agents is likely to be ineffective. Limited evidence exists to support the pharmacological management of persistent gut symptoms in quiescent IBD.

Dietary fermentable carbohydrates increase small intestinal water through osmotic potential (eg, fructose, mannitol) and colonic gas through microbial fermentation (eg, fructans, galacto-oligosaccharides [GOS]).[4] Randomized, crossover rechallenge trials, which overcome the limitations of masking and confounding in dietary intervention studies, have shown that fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) can induce gut symptoms in both IBS and quiescent IBD.[5,6]

Dietary restriction of FODMAPs (low FODMAP diet) is thought to ameliorate functional gut symptoms by reducing diet-induced luminal water and colonic gas and, consequently, luminal distension, in those with visceral hypersensitivity.[7,8] Randomized, placebo-controlled trials of low FODMAP diet in IBS, delivered through a feeding study or as dietary advice, reported improvement of gut symptoms in 70% and 57% of patients, respectively.[9,10] In IBD, retrospective and prospective uncontrolled studies suggest potential benefit of low FODMAP diet as a therapy for persistent gut symptoms,[11,12] and more recently, a randomized controlled trial reported that gut symptoms improved in 81% of patients with IBD during a low FODMAP diet compared with 46% in control.[13] However, the trial was unblinded, therefore cannot account for the considerable placebo response that occurs in both IBS and IBD,[14] particularly in response to diet interventions.

Low FODMAP diet reduces fermentable substrate in the colon, and in IBS this alters microbiome composition, resulting in reduced Bifidobacteria[9,15] and *Faecalibacterium prausnitzii*[16] abundance. Bifidobacteria abundance in the mucosal microbiome is positively associated with the proportion of interleukin 10 expressing dendritic cells in Crohn's disease (CD).[17] Furthermore, low abundance of *F prausnitzii* is associated with active IBD, and is associated with greater postoperative relapse at 6 months in CD.[18–20] Therefore, the microbiological impact of low FODMAP diet could theoretically have an adverse effect on the mucosal immune response and disease course in IBD, but to date has been investigated in only 1 trial of 9 patients with CD.[21]

Accordingly, clinical trials to establish the therapeutic benefit of low FODMAP diet in managing gut symptoms in IBD must be placebo-controlled and must assess the impact on the microbiome, GI inflammation, and disease activity. To this end, we designed a randomized controlled trial to investigate the effects of low FODMAP dietary advice compared with placebo (sham) dietary advice on persistent gut symptoms, disease activity, GI microbiome, and peripheral T-cell phenotypes in quiescent IBD.

Methods

Study Design and Participants

Patients were recruited from 2 large gastroenterology clinics in London, United Kingdom, in a multicenter, randomized, parallel, single-blinded, placebo-controlled trial. Eligible patients were aged $\geq$18 years, with quiescent CD or ulcerative colitis (UC), experiencing ongoing gut symptoms and were naïve to low FODMAP diet. Quiescent IBD was defined by all of the following: physician global assessment, stable medications, no IBD flare in the previous 6 months, fecal calprotectin $<$250 μg/g, and serum C-reactive protein (CRP) $<$10 mg/L. The threshold for fecal calprotectin was chosen according to evidence proposing optimal sensitivity and specificity for detecting endoscopically quiescent disease.[22] Ongoing gut symptoms were required to meet the Rome III criteria for either diarrhea predominant (IBS-D), mixed subtype (IBS-M), or unsubtyped IBS (IBS-U), functional bloating, or functional diarrhea, experiencing abdominal pain, bloating, and/or diarrhea on $\geq$2 days during the baseline screening week and reporting inadequate relief of GI symptoms.[23]

Patients with dose changes of azathioprine, mercaptopurine, methotrexate, or biologics in the preceding 12 weeks; oral 5-aminosalicylic acid in the preceding 4 weeks; or antibiotics, probiotics, or prebiotics in the preceding 8 weeks were excluded. Patients with pure perianal CD, a current stoma, previous extensive GI resection, or a current stricture were excluded. Patients with established bile acid malabsorption were excluded because gut symptoms relating directly to bile acid malabsorption may not be modifiable by low FODMAP diet. Patients with constipation-predominant symptoms were excluded, because low FODMAP diet could exacerbate this symptom. Patients with self-reported lactose intolerance were included if they continued to experience gut symptoms despite low lactose diet. Patients were excluded if they had significant comorbidities, or if they were pregnant or lactating.

Research ethics committee approval was received from the London Dulwich ethics committee (Reference 15/LO/1684) and the trial was registered on the ISRCTN registry (ISRCTN17061468) before participant recruitment. All authors had access to the study data and reviewed and approved the final manuscript.

Randomization and Masking

A random allocation sequence was prepared online (www.sealedenvelope.com) by an independent researcher using block randomization, with a 1:1 ratio of low FODMAP to placebo sham diet. Randomization was stratified by diagnosis (CD or UC) and fecal calprotectin at screening (≤100 μg/g and 101–249 μg/g). Allocation sequences were sealed in opaque envelopes.

Participants were blinded to diet allocation and informed that both diets would change the types of carbohydrates consumed, but that one was the diet under investigation, whereas the other was a sham diet. The terms "fermentable carbohydrates," "low FODMAP diet," or the mechanisms of the diet were not mentioned to participants.

Study Visits

Patients were identified via gastroenterology clinics and referrals to the dietetic department for the management of gut symptoms in quiescent IBD. Fecal calprotectin and CRP were assessed during screening, and a 7-day food, stool, and GI symptom diary was completed, from which the frequency and severity of gut symptoms were assessed for eligibility. Eligible participants attended a baseline visit, during which questionnaires were completed and stool and blood samples were collected to assess microbiome and immunology. Patients were randomized to follow either low FODMAP or sham dietary advice for 4 weeks and completed a 7-day food, stool, and GI symptom diary in the final week. Finally, all outcomes were reassessed at an end-of-trial visit that was conducted within 3 days of the end of the 4-week period, during which diet allocation was continued.

Intervention and Control

Low FODMAP and sham dietary advice were provided to all participants by the same research dietician (S.R.C.) with extensive training and experience in delivering low FODMAP diet. The diet involves the restriction of dietary fructans, GOS, lactose, fructose in excess of glucose, and polyols, including sorbitol and mannitol, and is described in detail elsewhere.[24] The selection of an appropriate control group and difficulties in masking intervention and control are challenging in dietary intervention studies, but for research on dietary advice (which most closely mimics clinical practice), "sham" dietary advice is considered gold standard.[25] The sham diet in this trial aimed to provide patients in the control group with an exclusion diet of similar intensity and burden to low FODMAP diet, while not affecting nutrient, fiber or FODMAP intakes. The sham diet has been used successfully in the only randomized, placebo-controlled trial of low FODMAP dietary advice in IBS.[9] Dietary counseling for both low FODMAP diet and sham diet lasted approximately 20 minutes and both groups received written information.

Dietary compliance to both diets was encouraged at weekly telephone contact. Compliance with the diet was assessed at end of the trial using the single question: "During the 4-week trial I have followed the diet…": never/rarely (<25% of the time), sometimes (25%–50% of the time), frequently (51%–75% of the time), or always (76%–100% of the time). For the purposes of per protocol (PP) analysis, compliance was defined as following diet "always" (76%–100% of the time) during the trial.

Outcomes

The primary outcome was the change in IBS Severity Scoring System (IBS-SSS) during the trial, compared between groups. Predefined secondary outcomes included other measures of gut symptoms (total IBS-SSS score, proportion of patients achieving a 50-point IBS-SSS reduction, global symptom question; GI symptom rating scale [GSRS]), disease-specific HR-QOL, stool frequency and consistency, clinical disease activity, inflammatory markers, dietary intake, microbiome composition and function, short chain fatty acid (SCFA) concentrations, and peripheral T-cell phenotype. All predefined secondary outcomes were included in the study protocol before study commencement. Exploratory outcomes included responders defined as achieving at least a 50% reduction in total IBS-SSS score during the trial.

Clinical Outcomes

Gut symptoms were evaluated at baseline and end of trial using the IBS-SSS[26] and the GSRS.[27] The global symptom question was used to assess adequate relief of GI symptoms at end of trial. Disease-specific HR-QOL was assessed using the UK-specific IBD questionnaire.[28] Stool frequency and consistency were measured using the Bristol Stool Form Scale,[29] which has undergone extensive validation.[30]

Disease Activity

At baseline and end of trial, disease activity was assessed using the Harvey-Bradshaw Index for CD[31] and the Partial Mayo Score for UC.[32] Patient-perceived IBD control was assessed in all patients using the IBD Control questionnaire.[33] Fecal calprotectin concentrations were determined using enzyme-linked immunosorbent assay and serum CRP concentrations were determined using a standard assay in the hospital laboratory.

Dietary Intake

Dietary intake was measured at baseline and end of trial using 7-day food records. A nutrient composition database (Nutritics, Dublin, Ireland) was used for assessment of nutrient and fiber intakes, and into a bespoke database to assess FODMAP intake (Monash University, Melbourne, Australia).

Microbiome Composition, Function, and SCFA

A quantitative metagenomic pipeline following the International Human Microbiome Standards (IHMS; http://www.microbiome-standards.org) was used to assess GI microbiome composition and function.[34]

A fresh stool sample was collected at baseline and end of trial and stored immediately on ice. The sample was homogenized and stored at −80°C (IHMS SOP 04 V2). DNA extraction was performed following IHMS SOP 07 V2. DNA was quantitated using Qubit Fluorometric Quantitation (ThermoFisher Scientific, Waltham, MA) and qualified on a

Fragment Analyzer (Agilent Technologies, Santa Clara, CA). The sequencing library was built using 3 μg of high molecular weight DNA (>10 kbp). DNA was sheared into fragments of approximately 150 base pairs (bp) using an ultrasonicator (Covaris, Woburn, MA) and fragment library construction was performed using the 5500 Solid Fragment 48 Library Core Kit (ThermoFisher Scientific). Fragment libraries were sequenced using the Ion Proton Sequencer (ThermoFisher Scientific), generating a minimum of 20 million high-quality reads of 150 bp per library. Gene abundance profiling was performed by mapping high-quality reads to the 9.9 million gene-integrated reference catalog of the human microbiome[35] using Bowtie 2 with a 95% identity threshold.[36] The gene abundance profiling table was generated via a 2-step procedure using METEOR. The gene abundance table was processed for rarefaction and normalization using the MetaOMineR (momr) R package.[37] To decrease technical bias due to different sequencing depth and artifacts of sample size on low abundance genes, read counts were rarefied to 14 million reads per sample by random sampling without replacement. The resulting rarefied gene abundance table was normalized according to the FPKM (fragments per kilobase of exon model per million reads mapped) strategy. Metagenomic species (MGS) are co-abundant gene groups with more than 500 genes corresponding to microbial species.[38] Taxonomical annotation was performed on all genes by sequence similarity using National Center for Biotechnology Information blast N; a species-level assignment was given if >50% of the genes matched the same reference genome of the National Center for Biotechnology Information database (November 2016 version) at a threshold of 95% of identity and 90% of gene length coverage. The remaining MGSs were assigned to a given taxonomic level from genus to superkingdom level, in which more than 50% of their genes had the same assignment level. Microbial gene richness (gene count) was calculated by counting the number of genes detected at least once in a given sample. MGS richness (MGS count) was calculated directly from the MGS abundance matrix.

The functional analysis is led using an MGP pipeline FantoMET (unpublished, 2018). Genes of the catalog were annotated using the Kyoto Encyclopedia of Genes and Genomes (KEGG)82 database. KEGG and Gut Metabolic Modules were reconstructed in each metagenomic species using their pathway structures (and potential alternative pathways).[39] Abundance of each detected module in a metagenomic species corresponds to the abundance of the metagenomic species as described in the method section. Abundance of a given module in a sample is computed as the sum of the abundances of the module in each metagenomic species.

Fecal SCFA concentrations were assessed using a standard gas-liquid chromatography protocol, using the 9890A series gas-liquid chromatography system (Agilent Technologies) and fecal pH was measured using a pH probe (InLab and FE20 FiveEasy Benchtop pH meter; Mettler Toledo, Columbus, OH).

Peripheral T-Cell Phenotype

Blood samples were collected at baseline and end of trial in sodium-heparin vacutainer tubes (BD Bioscience, San Jose, CA) and processed within 3 hours. Whole blood was labeled with fluorescently conjugated monoclonal antibodies to detect CD3 T cells, as well as naïve (CD45RA+) and effector/memory (CD45RA−) CD4 and CD8 T cells, and Vδ2 unconventional T cells. The gut-homing integrin $\alpha4\beta7$ was detected by labeling with anti-$\beta7$.[40,41] The BD FACSCanto II flow cytometer was used to acquire data, the FACS DIVA software (BD Bioscience) was used to collect the data, and Winlist software (Verity, Topsham, ME) was used to analyze the data.

Statistical Analysis

Sample size was calculated based on the primary outcome, with expected values taken from a previous trial in IBS comparing low FODMAP (mean IBS-SSS change −117 points, standard deviation [SD] 86) with sham advice (−44 points, SD 72).[9] With a power of 80% and 2-sided significance of 5%, a sample size of 44 participants was required. Assuming 15% attrition, a sample size of 52 participants (26 per group) was required.

Pre-planned comparisons of the primary (change in IBS-SSS score during trial) and secondary outcomes between the low FODMAP and sham diet at end of trial were performed. Subgroup analysis for UC and CD were pre-planned in the protocol and were conducted for all outcomes. The proportion of participants achieving at least a 50% reduction in total IBS-SSS score during the trial was an exploratory outcome compared between the diet groups.

Data on gut symptoms, HR-QOL, disease activity, inflammatory markers and peripheral T-cell phenotype were analyzed by intention-to-treat (ITT), followed by PP, the latter consisting of patients who completed the trial, did not violate protocol, and were "always" compliant with dietary intervention. Data on microbiome composition and SCFA concentrations are presented for the PP population.

Clinical variables, SCFA, and T-cell phenotype data were compared between groups at end of trial using analysis of covariance, with corresponding baseline values as a covariate, and are therefore presented as estimated marginal mean (standard error of the mean [SEM]). Categorical variables, presented as number (%), were compared between groups using the χ^2 or Fisher's Exact Test. Statistical analysis was performed using SPSS Version 24.0 (IBM, Chicago, IL).

Differences in gut microbial alpha and beta diversity between low FODMAP and sham diet were calculated using Mann-Whitney tests, whereas comparisons of taxonomical and functional composition were assessed using likelihood ratio tests. Microbiome composition was analyzed using 2 approaches. First, an untargeted analysis of the relative abundance of all characterized bacteria (a total of 616 species and strains) was performed. Then, a targeted analysis of the specific species and strains of interest with regard to the low FODMAP diet or IBD was performed. P values were adjusted for multiple comparisons using the Benjamini Hochberg approach for both the untargeted and targeted analyses. Microbiome bioinformatics was performed using R version 1.0.136 (Vienna, Austria). Differences are stated as statistically significant where $P \leq .05$.

Results

Recruitment occurred between February 2016 and May 2017. Of 155 screened participants, 103 were ineligible

(Supplementary Figure 1). Fifty-two patients were randomized to low FODMAP (n = 27) and sham diets (n = 25). All 52 randomized patients were included in the ITT analysis. Six participants were withdrawn; 2 withdrew consent during the trial (1 in each group), 1 became pregnant (sham diet), 2 commenced steroids due to an IBD flare (1 in each group), and 1 commenced antibiotics for an unrelated infection (low FODMAP diet). Of the 46 patients completing the trial, 3 were noncompliant with the diet, leaving 43 participants (21 low FODMAP diet, 22 sham diet) in the PP analysis.

Baseline characteristics are displayed in Table 1. There were no differences in IBD characteristics between diet groups. However, participants in low FODMAP group were younger (33, SD 11 years) than in the sham diet (40, SD 13 years, $P = .031$). There was a greater proportion of participants of white ethnicity in the low FODMAP (25/27, 92%) than the sham group (19/25, 76%, $P = .029$).

Adverse Events

There were 6 adverse events during the trial. Two participants had an IBD relapse (1 in each group) and 1 commenced antibiotics unrelated to IBD (low FODMAP). All 3 participants were withdrawn from the trial because of meeting exclusion criteria. One participant reported a worsening of abdominal pain lasting 2 days that resolved (sham diet). Flu-like symptoms and sinusitis were reported (1 in each group), both of which were unrelated to the diet. No serious adverse events were recorded.

Table 1. Baseline Demographic and IBD Characteristics of the Study Groups

Variable	Low FODMAP diet (n = 27)	Sham diet (n = 25)	*P*
Age (*yr*)	33 (11)	40 (13)	**.031**
Male, n (%)	10 (37)	13 (52)	.278
Body mass index (kg/m^2)	24 (3)	25 (4)	.526
Ethnicity, white, n (%)	25 (92)	19 (76)	**.029**
Rome III criteria, n (%)			.150
IBS-Diarrhea predominant	10 (37)	5 (20)	
IBS-Mixed subtype	2 (7)	2 (8)	
IBS-Unsubtyped	0 (0)	1 (4)	
Functional bloating	15 (56)	13 (52)	
Functional diarrhea	0 (0)	4 (16)	
Baseline IBS-SSS score	222 (76)	227 (81)	.847
CD, n (%)	14 (52)	12 (48)	.781
Time since diagnosis, *yr*	7 (8)	11 (11)	.187
Montreal classification			
Crohn's disease location, n (% of CD)			.773
Ileal	4/14 (29)	2/12 (17)	
Colonic	4/14 (29)	4/12 (33)	
Ileocolonic	6/14 (42)	6/12 (50)	
CD behavior, n (% of CD)			.949
Nonstricturing, nonpenetrating	9/14 (64)	8/12 (66)	
Stricturing	3/14 (21)	2/12 (17)	
Penetrating	2/14 (14)	2/12 (17)	
Perianal disease, n (% of CD)	4/14 (29)	3/12 (25)	1.000
UC extent, n (% of UC)			.403
Proctitis	6/13 (46)	3/13 (23)	
Left-sided	4/13 (31)	7/13 (54)	
Extensive	3/13 (23)	3/13 (23)	
Medication, n (%)			
Mesalamine	12 (44)	11 (44)	.974
Thiopurine	9 (33)	12 (48)	.282
Infliximab	10 (37)	4 (16)	.087
Adalimumab	2 (7)	4 (16)	.411
Vedolizumab	0 (0)	1 (4)	.481
Methotrexate	2 (7)	1 (4)	1.000
Clinical symptoms			
Total IBS-SSS score, mean (SD)	222 (76)	227 (81)	.847
Stool frequency, mean (SD)	1.8 (1.3)	2.1 (1.0)	.282
Stool consistency, proportion normal stools (type 3, 4, 5), mean (SD)	66 (29)	64 (32)	.869

NOTE. Continuous variables are presented as mean (SD) and were compared between groups using unpaired *t*-test, and categorical variables are presented as n (%) and were compared between groups using χ^2 test. Bold text indicates statistically significant *P* values ($P \leq .05$).

Table 2. IBS Severity Scoring System Scores, Global Symptom Question, and Stool Frequency and Consistency at End of Trial

	All participants			UC			CD		
	Low FODMAP diet (n = 27)	Sham diet (n = 25)	*P*	Low FODMAP diet (n = 13)	Sham diet (n = 13)	*P*	Low FODMAP diet (n = 14)	Sham diet (n = 12)	*P*
Change in IBS-SSS score, mean (SEM)	−67 (12)	−34 (13)	.075	−77 (15)	−29 (15)	**.031**	−55 (99)	−42 (43)	.515
Total IBS-SSS score, mean (SEM)	158 (12)	190 (13)	.075	135 (15)	183 (15)	**.031**	170 (96)	208 (95)	.515
Pain severity	22 (3)	30 (3)	.098	20 (4)	29 (4)	.123	24 (22)	32 (20)	.475
Days of pain (days)	36 (5)	38 (5)	.781	31 (6)	35 (6)	.645	36 (37)	48 (37)	.871
Bloating severity	23 (3)	34 (3)	**.021**	21 (4)	31 (4)	.113	22 (20)	39 (17)	.071
Satisfaction with bowels	39 (3)	47 (4)	.103	31 (5)	45 (5)	.068	52 (18)	43 (26)	.487
Impact on life	38 (3)	41 (3)	.521	34 (4)	41 (4)	.199	36 (25)	46 (25)	.799
IBS-SSS 50% reduction, n (%)	9 (33)	1 (4)	**.012**	4 (31)	0 (0)	.096	5 (36)	1 (8)	.170
Adequate relief, n (%)	14 (52)	4 (16)	**.007**	7 (54)	2 (15)	.097	7 (50)	2 (17)	.110
Stool frequency (per d), mean (SEM)	1.7 (0.1)	2.1 (0.1)	**.012**	1.8 (0.1)	2.0 (0.1)	.501	1.7 (0.1)	2.1 (0.1)	**.019**
Stool consistency									
Daily BSFS score, mean (SEM)	4.3 (0.2)	4.4 (0.2)	.606	4.0 (0.2)	4.4 (0.2)	.191	4.6 (0.2)	4.4 (0.2)	.673
Stool consistency, proportion normal stools (Type 3, 4, 5), mean proportion (SEM)	65 (5)	69 (5)	.478	66 (6)	73 (6)	.487	63 (6)	65 (7)	.815

NOTE. Continuous variables are presented as estimated marginal mean (SEM) and were compared between groups using an analysis of covariance with the corresponding baseline values as a covariate, and categorical variables are presented as n (%) and were compared between groups using χ^2 test. Bold text indicates statistically significant *P* values ($P \leq .05$).
BSFS, Bristol Stool Form Scale.

Gut symptoms and HR-QOL

There was a greater reduction in total IBS-SSS score following low FODMAP (−67, SEM 12) compared with sham diet (−34, SEM 13), although the difference was not statistically significant ($P = .075$) (Table 2). There was a significantly lower score for bloating severity (IBS-SSS) following low FODMAP (23, SEM 3) than sham diet (34, SEM 3, $P = .021$). The PP analysis showed similar results to the ITT analysis for all IBS-SSS outcomes. The exploratory analysis revealed that significantly more participants achieved a 50% reduction in IBS-SSS following low FODMAP (9/27, 33%) than sham diet (1/25, 4%, P=.012) (Table 2).

Predefined subgroup analyses of UC (n = 26) and CD (n = 26) were performed for all clinical outcomes (Table 2). In UC, there was a significantly greater reduction in IBS-SSS score following low FODMAP compared with sham diet ($P = .031$), as well as a significantly lower end-of-trial IBS-SSS score ($P = .031$). In CD, there was no difference in change in IBS-SSS score following low FODMAP compared with sham diet ($P = .515$), or in end-of-trial IBS-SSS score ($P = .515$).

Significantly more patients reported adequate relief of gut symptoms following low FODMAP (14/27, 52%) than sham diet (4/25, 16%, $P = .007$). There were no differences in the proportion of patients reporting adequate relief between low FODMAP and sham diet in the subgroup analysis of UC (7/13, 54% vs 2/13, 15%, $P = .097$) or CD (7/14, 50% vs 2/12, 17%, $P = .110$).

The severity of flatulence, as measured using the GSRS, was significantly lower during low FODMAP (0.9, SEM 0.1) compared with sham diet (1.2, SEM 0.1, $P = .035$); however, no other symptoms, including abdominal pain, were different between groups (Supplementary Table 1). Significantly lower daily stool frequency was reported following low FODMAP (1.7, SEM 0.1) than sham diet (2.1, SEM 0.1, $P = .012$), but there was no difference in the proportion of stools of normal consistency (types 3–5) between low FODMAP (65% normal consistency, SEM 5%) and sham diet (69%, SEM 5%, P=.478) (Table 2).

Total IBD questionnaire score was significantly greater (indicating better HR-QOL) following low FODMAP (81.9, SEM 1.2) than sham diet (78.3, SEM 1.2, $P = .042$). Specifically, the Bowel II domain score (effects of GI symptoms on HR-QOL) was significantly greater following low FODMAP (76.5, SEM 2.0) than sham diet (70.0, SEM 2.1, $P = .031$).

Disease Activity

At baseline, most participants had CRP <5 mg/L (50/52, 96%) and fecal calprotectin <100 μg/g (43/52, 83%).

In CD, there was no difference in Harvey-Bradshaw Index score between low FODMAP (3.2, SEM 0.4) and sham diet (3.4, SEM 0.5, $P = .814$) at end of trial. In UC, there was no difference in Partial Mayo score between low FODMAP (0.2, SEM 0.2) and sham diet (0.2, SEM 0.2, $P = .951$). The IBD-control score demonstrated greater patient-perceived control of IBD following low FODMAP (88.3, SEM 4.3) compared with sham diet (74.3, SEM 4.5, $P = .028$); these differences were seen specifically in UC (94.2, SEM 6.6 vs 71.3, SEM 6.6, $P = .022$) but not in CD (81.4, SEM 5.2 vs 79.1, SEM 5.7, $P = .768$).

Importantly, there was no difference in end-of-trial fecal calprotectin between low FODMAP (60.0 μg/g, SEM 9.4) and sham diet (59.6 μg/g, SEM 9.8, $P = .976$) or in serum CRP concentration between low FODMAP (2.0 mg/L, SEM 0.3) and sham diet (1.6 mg/L, SEM 0.3, $P = .246$).

Further fecal calprotectin concentration data (including UC and CD subgroup analyses and baseline compared with end-of-trial comparisons) are presented in Supplementary Table 2.

Dietary Intake and Compliance

In low FODMAP and sham diet groups, 24 (88%) of 27 and 25 (100%) of 25 participants reported following the diet "always" (76%–100% of the time) ($P = .230$). In support of high levels of self-reported compliance, intakes of fructans, GOS, lactose, excess fructose, sorbitol, and mannitol were significantly lower in the low FODMAP compared with sham diet (Supplementary Table 3).

Seven-day food diaries revealed significantly lower energy, protein, fat, sugars, calcium, phosphorus, and iodine intake in low FODMAP compared with sham diet (Supplementary Table 3). There were no significant differences in intakes of any other nutrients between diet groups.

Microbiome Composition, Function, and SCFA

An average of 22,690,418 sequencing reads of 150 bp were obtained for each sample, with an average 14,310,652 reads mapping uniquely to the gene catalog (67% of reads).

There was no difference in gene count, species count, phyla distribution, or any index of α-diversity or β-diversity between diet groups at end of trial (Figure 1*A–D*).

Of 616 species present in more than 5% of subjects, the abundance of 29 species (4.7%) was significantly affected ($P \leq .05$) by the diet (untargeted microbiome analysis) (Figure 2). None of these remained significant when adjusted for multiple comparisons. In the targeted microbiome analysis (Table 3), relative abundance of total Bifidobacteria was not significantly different between low FODMAP and sham diet ($P = .073$); however, *Bifidobacterium longum* ($P = .005$, $Q = .017$) and *Bifidobacterium adolescentis* ($P = .003$, $Q = .017$) were significantly lower, and *Bifidobacterium dentium* abundance was higher ($P = .035$, $Q = .096$) following the low FODMAP diet. Abundance of total *F prausnitzii* species was significantly lower following low FODMAP compared with sham diet ($P = .038$). However, no *F prausnitzii* strains were significantly lower and, interestingly, *F prausnitzii* SL3/3-M21/2 was higher following low FODMAP compared with sham diet (Table 3).

Differences in microbial abundance in the UC and CD subgroup analyses are presented in the Supplementary Table 4.

The metabolic potential of the microbiome was assessed using functional metagenomics. The abundance of 34 KO (KEGG orthology) groups were significantly different

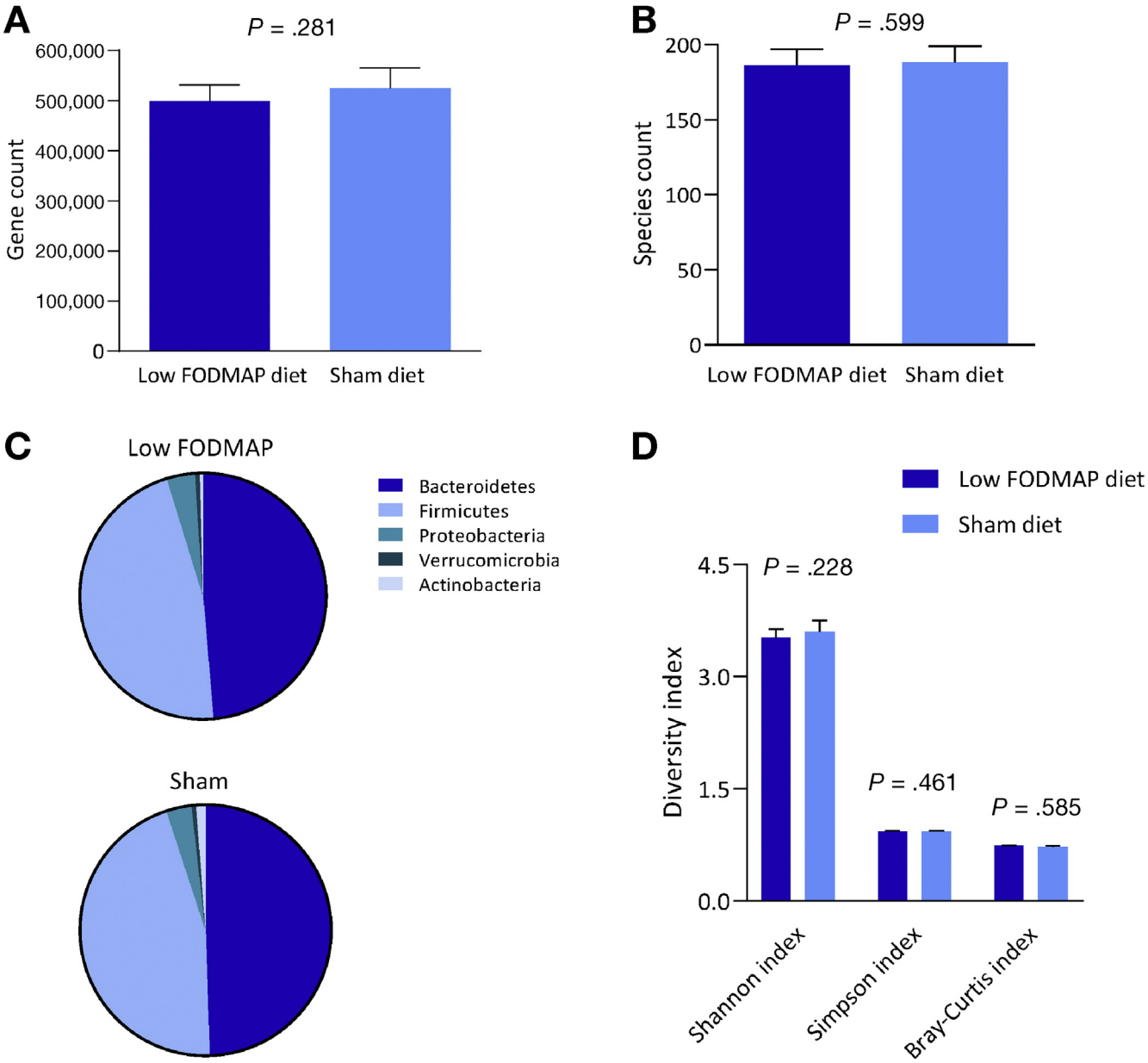

Figure 1. Alpha and beta diversity and phyla distribution at end of trial. (*A*) Microbial gene richness. (*B*) Microbial species richness. (*C*) Phyla distribution. (*D*) Shannon index, Simpson index, and Bray-Curtis index.

($P \leq .05$) between low FODMAP and sham diet groups (Figure 3). Among the modules significantly higher in abundance following low FODMAP compared with sham diet were cellobiose transport system and propionate production, and among modules lower in abundance were lactose and galactose degradation pathways and glutamate transport system and the putative zinc/manganese transport system. None of these remained significant following false discovery rate (FDR) correction.

There were lower fecal concentrations of total SCFA following low FODMAP (398 mg/100 g feces, SEM 37) compared with sham diet (505 mg/100 g feces, SEM 36, $P = .049$) in the PP population. In UC, total SCFAs were significantly lower following low FODMAP (386 mg/100 g feces, SEM 53) than sham diet (553 mg/100 g feces, SEM 55, $P = .041$); however, in CD there was no difference between diet groups (409 mg/100 g feces, SEM 51) and sham diet (463 mg/100 g feces, SEM 46, $P = .453$). Individual SCFA concentrations and fecal pH in the ITT and PP populations, and in UC and CD, are provided in the Supplementary Table 5.

Peripheral T-Cell Phenotype

There were no differences in absolute numbers or proportions of circulating naïve or effector/memory CD4 and CD8 T-cell subsets, or in cells within these subsets expressing $\alpha 4\beta 7$, between diet groups at the end of the trial (Supplementary Table 6). Although there was no difference in the total number of Vδ2 T cells between groups, there

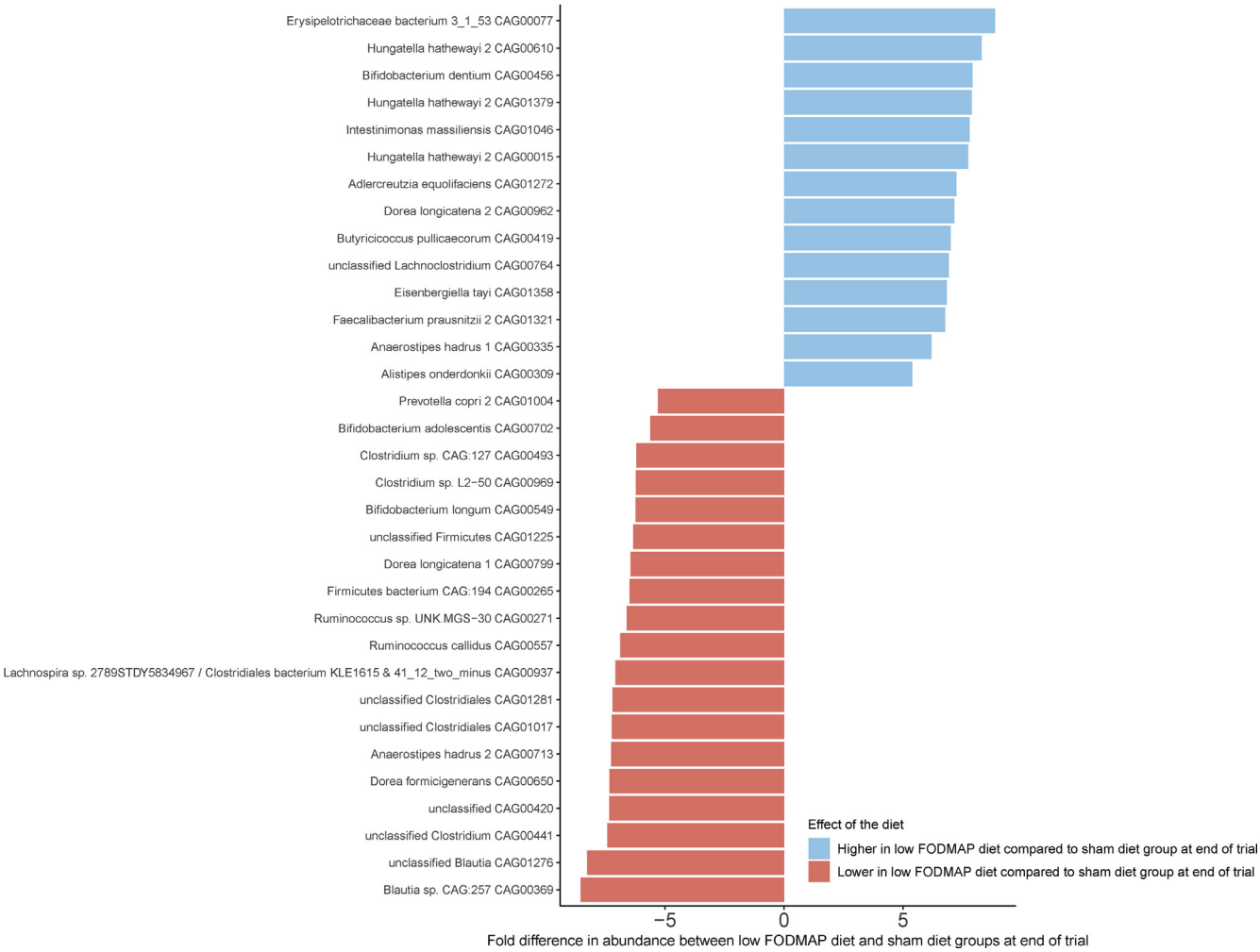

Figure 2. Untargeted microbiome analysis: fold difference in abundance of 33 species that were significantly different ($P < .05$) between diet groups at end of trial. None of these remained significant after FDR correction

were significantly fewer $\alpha4\beta7$ positive Vδ2 T cells following low FODMAP compared with sham diet (Supplementary Table 6).

Discussion

This is the first randomized, placebo-controlled trial demonstrating that low FODMAP dietary advice improves aspects of gut symptoms and HR-QOL in patients with quiescent IBD compared with sham dietary advice. Low FODMAP diet did not alter overall microbiome diversity or any species or strains on an untargeted analysis, although it altered some immune-regulatory components of the GI microbiome during a targeted analysis. Nonetheless, there was no impact on clinical disease activity or markers of inflammation.

The finding of no significant difference in change in IBS-SSS despite higher rates of adequate relief following low FODMAP diet contrasts with a recent trial in IBS that reported a significant reduction in IBS-SSS but no difference in adequate relief.[9] The effectiveness of low FODMAP diet in the current trial confirms the findings of a nonblinded randomized controlled trial in IBD in which more patients responded to low FODMAP diet than the normal diet group,[13] although the IBS-SSS response rate to low FODMAP diet in the current trial was significantly lower, which likely relates to the lack of blinding in the previous trial.

The subgroup of patients with UC, but not CD, reported a significantly greater reduction in IBS-SSS score after low FODMAP compared with sham diet. Differing efficacy of drug[42] and dietary[43] interventions has been demonstrated between CD and UC previously, and may be explained by differing disease pathophysiology and location. Furthermore, patients with CD are more likely to have intestinal inflammation not detected through fecal calprotectin,[44] which could have abrogated GI symptom responses to the diet. This subgroup analysis, although planned a priori, should be interpreted with caution because the trial was not powered for this comparison.

As expected from the proposed mechanism of action of low FODMAP diet, and consistent with previous studies in both IBS and IBD,[9–10,13,15] the greatest impact was on bloating and flatulence. Interestingly, abdominal pain was not different between diet groups following the diet. Unlike

Table 3. Targeted Microbiome Analysis: Relative Abundance of *Bifidobacteria* Species and *Faecalibacterium prausnitzii* Strains Between Diet Groups at End of Trial

	Low FODMAP diet (n = 21)	Sham diet (n = 22)	*P*	*Q*-value
Bifidobacteria (total)	8.63^{-7} (4.41^{-7})	3.19^{-6} (3.59^{-6})	.073	-[a]
Bifidobacterium adolescentis	1.99^{-7} (2.78^{-7})	2.55^{-6} (5.48^{-6})	**.003**	**.017**
Bifidobacterium longum	1.24^{-7} (1.81^{-7})	6.95^{-7} (1.03^{-6})	**.005**	**.017**
Bifidobacterium animalis	1.87^{-9} (8.59^{-9})	1.00^{-8} (4.58^{-8})	.746	.768
Bifidobacterium bifidum	6.77^{-8} (1.35^{-7})	1.79^{-7} (3.38^{-7})	.066	.146
Bifidobacterium breve	2.39^{-8} (1.09^{-7})	2.21^{-9} (1.09^{-7})	.768	.768
Bifidobacterium dentium	1.68^{-8} (5.23^{-8})	4.72^{-9} (1.75^{-8})	**.035**	.096
Bifidobacterium pseudocatenulatum	3.55^{-8} (1.17^{-7})	1.48^{-7} (4.42^{-7})	.473	.651
Faecalibacterium prausnitzii (total)	1.12^{-5} (1.42^{-5})	1.65^{-5} (1.35^{-5})	**.038**	-[a]
F prausnitzii A2-165	2.33^{-6} (1.93^{-6})	2.81^{-6} (2.81^{-6})	.186	.341
F prausnitzii SL3/3-M21/2	1.52^{-6} (2.08^{-6})	1.35^{-6} (1.68^{-6})	**.003**	**.017**
F prausnitzii L2-6	3.61^{-6} (4.26^{-6})	1.30^{-6} (1.32^{-6})	.750	.768
F prausnitzii cf. KLE1255	2.68^{-6} (3.48^{-6})	3.41^{-6} (3.89^{-6})	.310	.488

NOTE. All data are presented as mean (SD) relative abundance and were compared between groups adjusted for baseline abundance and end-of-trial stool consistency. Bold text indicates statistically significant *P* values ($P \leq .05$).
[a]Total Bifidobacteria and *F prausnitzii* abundance were not adjusted for multiple comparisons because these were analyzed separately at the genus level.

IBS, there is only limited evidence that abdominal pain in quiescent IBD relates to luminal distension.[45] Furthermore, at trial entry, 62% of participants fulfilled functional bloating or functional diarrhea criteria, but not IBS, and therefore had minimal abdominal pain.

In both the untargeted and targeted microbiome analyses, the abundance of fecal *B longum*, *B adolescentis,* and total *F prausnitzii* were lower following low FODMAP compared with sham diet, in agreement with the findings of some previous IBS trials,[9,16] but in contrast with a previous trial in which no changes in these bacteria were demonstrated in a small (n = 9) subgroup of patients with CD following low FODMAP diet.[21] Following adjustment for multiple comparisons, these findings remained significant in only the targeted microbiome analysis, as a result of fewer comparisons. These microbial alterations are likely a result of changes in colonic fermentable substrate; Bifidobacteria preferentially ferment fructans and GOS, whereas *F prausnitzii* indirectly use them through cross-feeding.[46]

The reduction in Bifidobacteria and *F prausnitzii* during low FODMAP diet are of potential concern, as these bacteria have immune-regulatory effects, including consistent

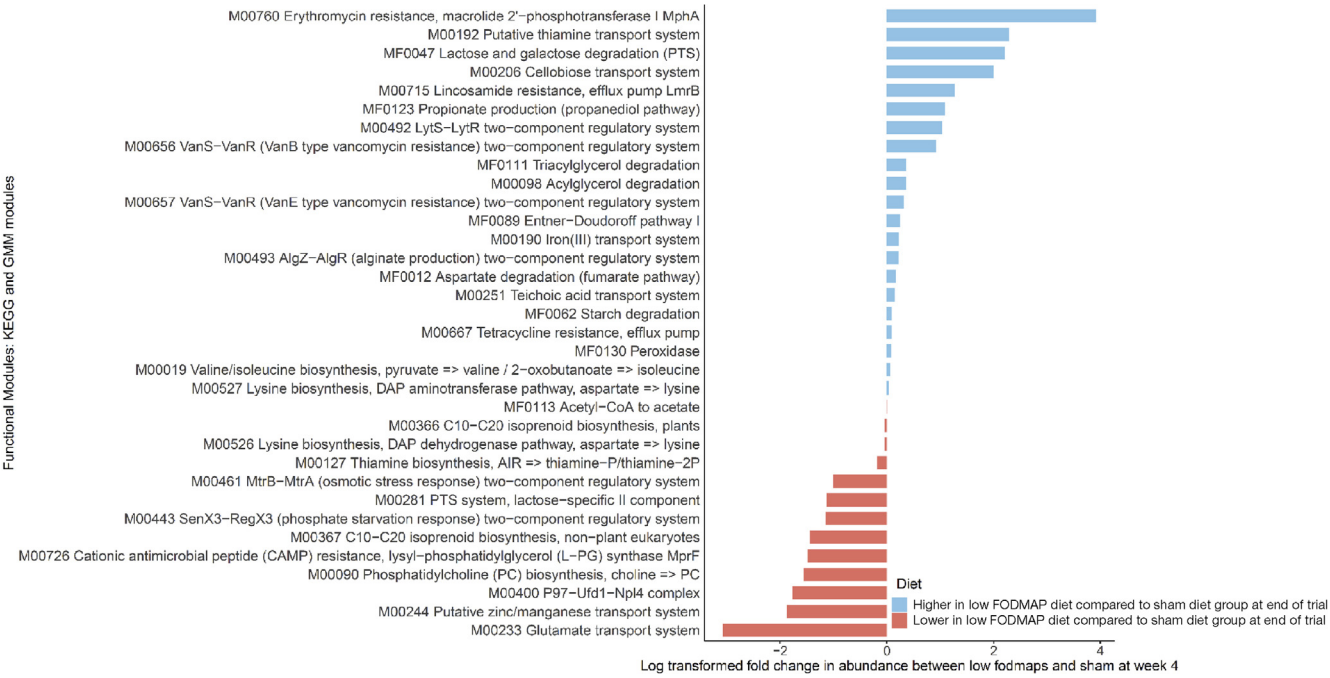

Figure 3. Fold difference in abundance of 34 functional modules with significantly different ($P < .05$) abundance between diet groups at end of trial. None of these remained significant after FDR correction.

evidence that Bifidobacteria and *F prausnitzii* increase peripheral blood mononuclear cell interleukin 10 production in vitro.[18,47] Furthermore, *F prausnitzii* is associated with lower postoperative CD recurrence.[18] Despite this, there were no detrimental effects of low FODMAP diet on fecal calprotectin or CRP. The lower proportion of $\alpha 4\beta 7+$ V$\delta 2+$ T cells following low FODMAP diet may relate to variability in and the possible effect of thiopurine exposure on V$\delta 2+$ T-cell numbers between individuals,[48] because there was no difference in absolute numbers of this T-cell subgroup between diet groups.

The lack of effect of low FODMAP diet on inflammation, despite microbiome alterations, may be explained in several ways. First, much of the evidence of immune-regulatory effects of *F prausnitzii* relate to strain A2-165,[18,49] which was not different between diet groups. Second, other GI bacteria, such as *Roseburia intestinalis* and *Lactobacillus* species, also exert immune-modulatory effects and were not altered by the diet.[47,50] Finally, the impact of longer-term restriction on inflammation in IBD is unknown because trial duration was 4 weeks.

Abundance of hydrogen-consuming *Adlercreutzia equolifaciens* was higher following low FODMAP compared with sham diet, confirming findings in IBS.[51] An emerging hypothesis is that low FODMAP diet may reduce luminal gas through both reduced fermentation and increased abundance of hydrogen-consuming bacteria; however, this requires confirmation.

The reduced SCFA concentrations in UC specifically may be explained by differences in baseline microbiome composition between UC and CD[52] and also the greater GI symptom responses to low FODMAP diet in UC. Furthermore, because the colon is the site of SCFA generation, the degree of colonic disease involvement may contribute to differences in SCFA generation between CD and UC. It is tempting to speculate that the UC microbiome possesses greater saccharolytic potential, which is thus more likely to respond to reduced fermentable substrate with a decline in GI symptoms and a concomitant decline in SCFA. However, this requires confirmation in studies powered to detect differential effects of the diet in UC and CD.

The analysis revealed differing abundance in numerous microbial genomic functional pathways between diet groups at end of trial. The abundance of acetyl-CoA to acetate pathway was lower following low FODMAP diet, in line with lower fecal acetate concentrations (Supplementary Information). Although fecal propionate concentrations were not affected by diet, the abundance of propionate production pathway was greater following low FODMAP diet.

A major strength of this trial is that low FODMAP dietary advice was compared with sham dietary advice, providing the first placebo-controlled evidence of effectiveness in IBD. Unlike feeding studies, which are ideal for proof-of-concept, the current trial methodology assessed the effectiveness of a dietary intervention as used in clinical practice. This trial also represents the first use of metagenomic sequencing providing a comprehensive assessment of GI microbiome composition and functional potential following low FODMAP diet. Furthermore, this is the first assessment of the effects of low FODMAP diet on immune function in IBD.

The trial design did not permit blinding of the investigator to treatment allocation. Furthermore, the observed alterations in certain nutrient intakes following low FODMAP diet, as demonstrated in previous low FODMAP diet trials,[53,54] may be confounders in interpreting the effects of low FODMAP diet in this trial. Finally, although not all patients fulfilled the IBS criteria at baseline, the IBS-SSS was chosen for gut symptom assessment because it encompasses the predominant symptoms of IBS (abdominal pain/altered bowel habit), functional bloating (bloating/distension), and functional diarrhea (altered bowel habit).

Quiescent IBD was defined, in part, as having fecal calprotectin $\leq$250 μg/g, as this has been shown to have optimal sensitivity and specificity for the identification of quiescent IBD.[22] Theoretically, this may have resulted in recruitment of some participants with very mildly active disease. However, only 16 (31%) of 52 had a fecal calprotectin above 50 μg/g and 9 (17%) of 52 above 100 μg/g at enrollment, thus likely having minimal effects on trial outcomes.

In conclusion, the first randomized, placebo-controlled dietary advice trial of low FODMAP diet in quiescent IBD reports improvement in some GI symptoms and HR-QOL. Despite a decline in Bifidobacteria and *F prausnitzii* abundance, the diet did not adversely affect disease activity. Therefore, we propose that a 4-week low FODMAP diet with expert advice and intensive follow-up is safe and effective in the management of persistent gut symptoms in quiescent IBD, but caution should be taken in longer-term use.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2019.09.024.

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Acknowledgments
Author contributions: SRC and KW were grant holders; SRC, JOL, AJS, MCL, PMI, and KW conceived and designed the study; SRC, PMI, and JOL recruited participants; SRC collected, collated, and analyzed the data; KW supervised data analysis; SRC and KW interpreted the data; SRC, AJS, and NEM performed flow cytometry and analysis; SF, SBI, NM, NP, HR, NG, FL, and SDE advised on and performed metagenomic sequencing and bioinformatics analysis; SRC wrote the manuscript; KW performed extensive editing of the manuscript; all authors reviewed and approved the final manuscript for submission.

Conflicts of interest
These authors disclose the following: Kevin Whelan and Miranda C. Lomer are the co-inventors of a mobile application to assist patients following the low FODMAP diet. Kevin Whelan has received consultancy fees from Danone, and a research grant from Clasado. The remaining authors disclose no conflicts.

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Supplementary Methods

Microbiome Composition and Function

The gene abundance profiling table was generated via a 2-step procedure using METEOR. First, reads uniquely mapping to a gene in the catalog were attributed to their corresponding genes. Second, reads mapped to multiple shared genes in the catalog were attributed according to the ratio of the unique mapping counts of the genes.

The 9.9 million–gene catalog was constructed by clustering 1436 MGS from 1267 human gut microbiome samples, as previously described.[1] MGS abundances were estimated as the mean abundance of the 50 genes defining a robust centroid of the cluster.

Supplementary Results

Gut Symptoms

The incidence of moderate or severe GI symptoms and 7-day severity of symptoms (as assessed using the GSRS) is presented in Supplementary Table 1. There were no differences between the diet groups in the incidence or severity of any symptoms, except for lower flatulence severity following low FODMAP compared with sham diet

Dietary Intake

Daily intakes of energy, protein, fat, sugars, calcium, phosphorus, and iodine were significantly lower following the low FODMAP compared with sham diet at end of trial (Supplementary Table 2).

There were no differences in the proportion of patients meeting national macronutrient, micronutrient and fiber recommendations between the low FODMAP and sham diet groups at end of trial, or between baseline and end of trial in either diet group (data not shown).

Microbiome Composition and SCFA

Supplementary Table 3 displays the relative abundance of the bacterial species or strains that were significantly different between the diet groups at end of trial in the untargeted UC and CD subgroup microbiome analyses.

There were no differences in α-diversity or β-diversity between the diet groups in UC or CD (data not shown).

There were no differences in concentrations of individual fecal SCFAs between diet groups at end of trial in the ITT population (Supplementary Table 4). However, in the PP population, there were significantly lower concentrations of total SCFAs following low FODMAP diet compared with sham diet (Supplementary table 4). Specifically, fecal acetate was significantly lower following low FODMAP diet compared with sham diet.

In patients with UC on the low FODMAP diet, compared with sham diet, there were lower concentrations of acetate (209 mg/100 g, SD 109 vs 328 mg/100 g, SD 154, $P = .037$), butyrate (66 mg/100 g, SD 40 vs 111 mg/100 g, SD 75, $P = .050$) and valerate (6 mg/100 g, SD 4 vs 13 mg/100 g, SD 10, $P = .044$) in the PP population. In patients with CD, there was a significantly lower end-of-trial isobutyrate concentration following the low FODMAP diet (7 SD 3 mg/100 g) compared with the sham diet (11 mg/100 g, SD 3, $P = .024$). There were no differences in the concentrations of any other individual SCFA in patients with CD in the PP population (data not shown).

Peripheral T-Cell Phenotype

There were no differences in proportion of T cells expressing $\alpha4\beta7$ between diet groups in patients with UC. In CD there were significantly fewer naïve CD4+ T cells (58.2%, SEM 4.5% vs 79.8%, SEM 5.7%; $P = .008$), naïve CD8+ T cells (62.6%, SEM 4.0% vs 76.4%, SEM 4.9%; $P = .042$) and effector/memory CD8+ T cells (59.5%, SEM 3.0% vs 70.3%, SD 3.7%; $P = .036$) expressing $\alpha4\beta7+$ on low FODMAP compared with sham diet.

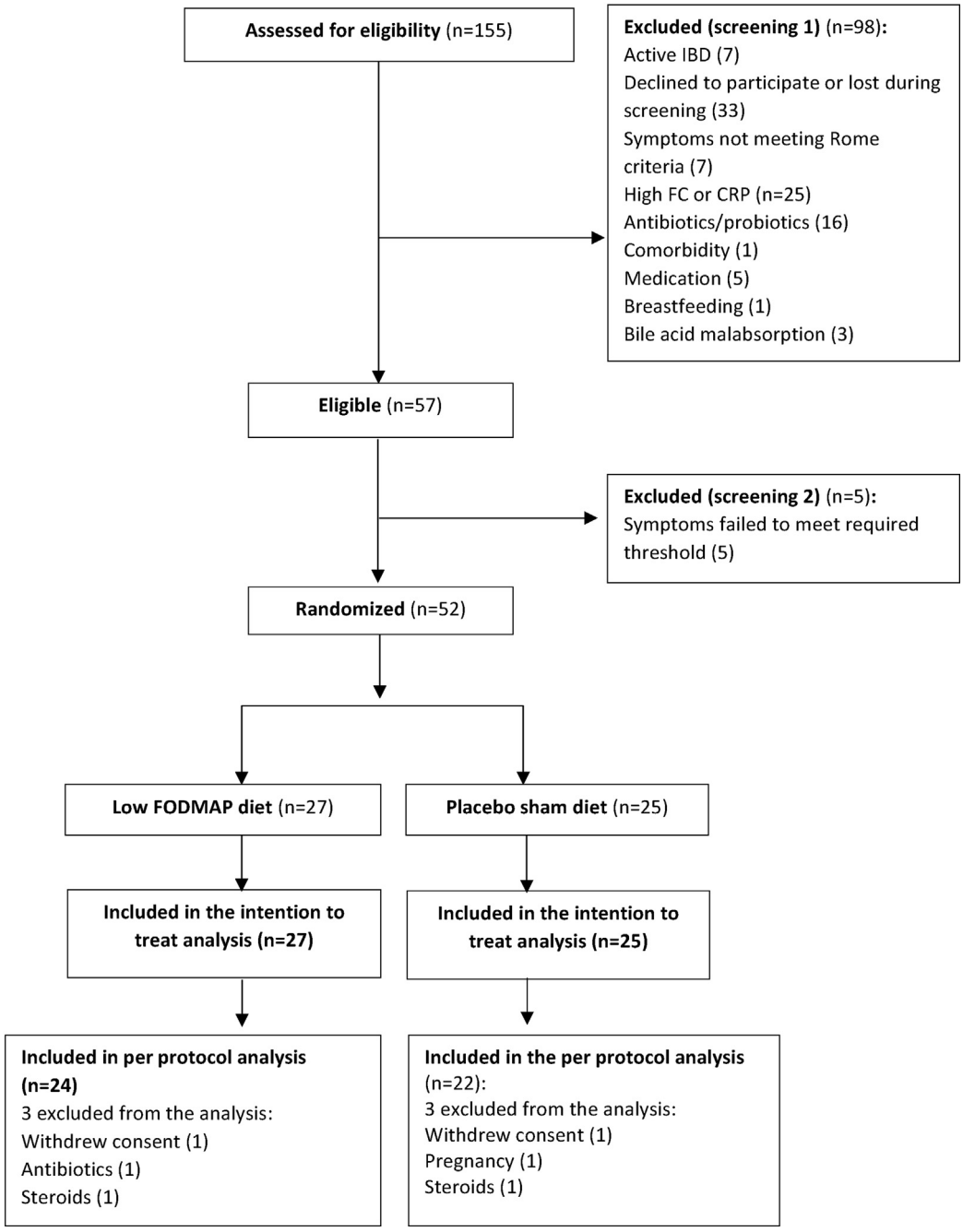
Fecal Calprotectin Between Baseline and End of Trial

There was no difference in fecal calprotectin concentrations between low FODMAP and sham diet groups at end of trial in either the CD (61.2 μg/g SEM 6.3 vs 68.4 μg/g SEM 6.8, $P = .448$) or the UC (55.9 μg/g SEM 18.2 vs 54.2 μg/g SEM 18.2, $P = .950$) subgroups.

There were no differences in fecal calprotectin at baseline compared with end of trial in low FODMAP or sham diet groups, and the same was true for the UC and CD subgroups (Supplementary Table 6).

Supplementary Reference

1. Nielsen HB, Almeida M, Juncker AS, et al. Identification and assembly of genomes and genetic elements in complex metagenomic samples without using reference genomes. Nat Biotechnol 2014;32:822.



Supplementary Figure 1. CONSORT diagram of participant flow through the trial.

Supplementary Table 1. Incidence and Severity of GI symptoms, as measured by the GSRS, at end of trial

	Incidence of moderate or severe symptoms[a]			Severity of GI symptoms[b]		
Symptom	Low FODMAP diet (n = 27)	Sham diet (n = 25)	*P*	Low FODMAP diet (n = 27)	Sham diet (n = 25)	*P*
Pain	1.5 (0.3)	1.1 (0.3)	.220	0.9 (0.5)	0.7 (4.5)	.243
Heartburn	0.3 (0.1)	0.2 (0.1)	.514	0.2 (0.5)	0.1 (0.3)	.344
Acid regurgitation	0.3 (0.1)	0.2 (0.1)	.359	0.2 (0.5)	0.2 (0.5)	.504
Nausea	0.5 (0.1)	0.3 (0.1)	.283	0.3 (0.5)	0.3 (0.5)	.335
Gurgling	0.7 (0.2)	0.8 (0.2)	.858	0.6 (0.5)	0.6 (0.5)	.995
Bloating	1.4 (0.3)	1.7 (0.3)	.595	0.9 (0.5)	0.9 (0.5)	.628
Belching	0.2 (0.1)	0.5 (0.1)	.141	0.4 (0.5)	0.5 (0.5)	.312
Flatulence	1.4 (0.3)	2.1 (0.4)	.152	0.9 (0.5)	1.1 (0.6)	**.035**
Constipation	0.5 (0.2)	0.6 (0.2)	.768	0.3 (0.5)	0.3 (0.5)	.513
Diarrhoea	0.4 (0.1)	0.5 (0.1)	.507	0.2 (0.5)	0.3 (0.5)	.214
Loose stools	0.9 (0.2)	0.9 (0.2)	.914	0.5 (0.5)	0.5 (0.5)	.981
Hard stools	0.1 (0.1)	0.3 (0.1)	.293	0.2 (0.4)	0.2 (0.5)	.656
Urgency	0.9 (0.2)	0.8 (0.2)	.756	0.6 (0.5)	0.5 (0.5)	.635
Incomplete evacuation	0.7 (0.2)	0.5 (0.2)	.592	0.5 (0.5)	0.4 (0.5)	.166
Tiredness	2.3 (0.3)	2.0 (0.4)	.692	1.1 (0.5)	1.0 (0.5)	.694
Overall symptoms	1.2 (0.5)	1.7 (0.7)	.439	1.0 (0.5)	1.1 (0.5)	.493

NOTE. Data are presented as estimated marginal mean (SEM) and groups were compared using analysis of covariance with baseline values as a covariate.
[a]Number of days on which each symptom was reported at moderate or severe during the final week of the diet.
[b]Average severity across 7 days: 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

Supplementary Table 2. Baseline Compared With End-of-Trial Fecal Calprotectin Concentrations in the Low FODMAP and Sham Diet Groups in All Patients and the UC and CD Subgroups

	All patients (low FODMAP n = 27, sham n = 25)			UC (low FODMAP n = 13, sham n = 13)			CD (low FODMAP n = 14, sham n = 12)		
	Baseline	End of trial	*P*	Baseline	End of trial	*P*	Baseline	End of trial	*P*
Low FODMAP (*μg/g*)	54.8 (84.8)	53.3 (84.8)	.857	21.9 (69.7)	10.9 (30.7)	.087	22.8 (66.1)	35.2 (26.8)	.674
Sham (*μg/g*)	70.9 (117.3)	66.9 (106.4)	.727	25.2 (67.3)	28.6 (67.7)	.721	22.8 (52.5)	15.9 (87.8)	.929

NOTE. Data are presented as median (interquartile range) and were compared between baseline and end of trial using a Wilcoxon signed rank test.

Supplementary Table 3. Daily Intake of Nutrients and FODMAPs in the Diet Groups at End of Trial (7-day Average Intakes)

	Low FODMAP diet (n = 27)	Sham diet (n = 25)	*P*
Energy (*kcal/d*)	1697 (47)	1918 (49)	**.002**
Protein (*g/d*)	74 (2)	83 (2)	**.008**
Fat (*g/d*)	68 (4)	80 (4)	**.035**
Saturated fat (*g/d*)	24 (1)	27 (2)	.102
Carbohydrate (*g/d*)	180 (6)	197 (6)	.058
Starch (*g/d*)	116 (4)	117 (5)	.841
Sugars (*g/d*)	63 (4)	76 (4)	**.022**
Fiber, AOAC (*g/d*)	17.8 (0.8)	19.2 (0.9)	.249
Calcium (*mg/d*)	692 (39)	911 (41)	**<.001**
Iron (*mg/d*)	10.9 (0.6)	12.0 (0.6)	.170
Zinc (*mg/d*)	9 (1)	10 (1)	.470
Sodium (*mg/d*)	1532 (85)	2195 (89)	**<.001**
Potassium (*mg/d*)	2938 (148)	3034 (154)	.658
Phosphorus (*mg/d*)	1140 (36)	1312 (37)	**.002**
Magnesium (*mg/d*)	290 (13)	297 (13)	.709
Iodine (*μg/d*)	124 (15)	176 (16)	**.022**
Selenium (*μg/d*)	59 (4)	57 (4)	.823
Vitamin A (*μg/d*)	1358 (207)	1328 (215)	.921
Vitamin C (*mg/d*)	90 (7)	75 (8)	.166
Vitamin D (*μg/d*)	6.4 (0.4)	6.3 (0.4)	.818
Vitamin B_9 (folate) (*μg/d*)	229 (12)	257 (12)	.110
Vitamin B_{12} (cobalamin) (*μg/d*)	6.0 (0.9)	5.6 (0.9)	.782
FODMAPs			
Fructans (*g/d*)	1.3 (0.2)	2.9 (0.2)	**<.001**
GOS (*g/d*)	0.4 (0.1)	0.8 (0.1)	**<.001**
Lactose (*g/d*)	5.6 (1.0)	10.9 (1.1)	**.001**
Excess fructose (*g/d*)	0.5 (0.2)	1.4 (0.2)	**.001**
Sorbitol (*g/d*)	0.1 (0.1)	0.6 (0.1)	**.001**
Mannitol (*g/d*)	0.1 (0.0)	0.3 (0.0)	**.002**

NOTE. Data are presented as estimated marginal mean (SEM) and groups were compared using analysis of covariance with baseline values as a covariate.
AOAC, Association of Official Analytical Chemists.

Supplementary Table 4. Untargeted Microbiome Analysis: Relative Abundance of Species and Strains That Were Significantly Different Between the Diet Groups ($P \leq .05$) at End of Trial in Patients With UC and CD

	UC				CD			
Genus or species	Low FODMAP diet (n = 13)	Sham diet (n = 11)	*P*	*Q*-value	Low FODMAP diet (n = 8)	Sham diet (n = 11)	*P*	*Q*-value
Bifidobacterium adolescentis	1.52^{-7} (2.65^{-7})	1.72^{-7} (2.79^{-6})	**.004**	.592	2.73^{-7} (3.02^{-7})	3.31^{-6} (7.19^{-6})	.216	.690
Bifidobacterium longum	1.60^{-7} (2.18^{-7})	7.21^{-7} (1.13^{-6})	**<.001**	.115	6.53^{-8} (7.46^{-8})	6.73^{-7} (9.83^{-7})	.201	.682
Faecalibacterium prausnitzii								
SL3/3-M21/2	1.30^{-6} (1.93^{-6})	1.55^{-6} (1.47^{-6})	**.017**	.592	1.87^{-6} (2.39^{-6})	1.17^{-6} (1.90^{-6})	**.031**	.654
A2-165	2.38^{-6} (2.02^{-6})	2.97^{-6} (2.35^{-6})	.563	.806	2.26^{-6} (1.91^{-6})	2.66^{-6} (3.29^{-6})	.094	.654
L2-6	3.76^{-6} (4.67^{-6})	1.68^{-6} (1.19^{-6})	.356	.693	3.37^{-6} (3.79^{-6})	9.56^{-7} (1.39^{-6})	.443	.752
KLE1255	3.63^{-6} (4.14^{-6})	4.43^{-6} (3.81^{-6})	.562	.806	1.13^{-6} (8.88^{-7})	2.48^{-6} (3.89^{-6})	**.025**	.654
Ruminococcus sp. UNK.MGS-30	0.00 (0.00)	5.14^{-7} (9.13^{-7})	**.024**	.592	0.00 (0.00)	0.00 (0.00)	.393	.729
Ruminococcus bicirculans	8.78^{-7} (2.18^{-6})	2.97^{-6} (5.15^{-6})	**.005**	.592	1.40^{-6} (2.58^{-6})	1.05^{-6} (1.97^{-6})	.984	.993
Ruminococcaceae unclassified CAG00957	2.19^{-8} (7.21^{-8})	1.44^{-8} (3.49^{-8})	**.010**	.592	1.63^{-9} (4.61^{-9})	1.31^{-7} (4.10^{-7})	.475	.768
Clostridium sp. AT4	4.91^{-7} (1.44^{-6})	5.35^{-8} (9.36^{-8})	**.015**	.592	1.02^{-7} (2.10^{-7})	1.31^{-7} (3.51^{-7})	.596	.849
Clostridium unclassified CAG00441	3.44^{-8} (3.72^{-8})	7.92^{-8} (1.31^{-7})	.107	.592	2.63^{-8} (1.89^{-8})	5.95^{-8} (1.30^{-7})	**.009**	.563
Clostridium bolteae	1.01^{-6} (2.99^{-6})	3.87^{-8} (4.40^{-8})	**.049**	.592	5.41^{-8} (2.71^{-7})	2.04^{-7} (2.71^{-7})	.800	.966
Clostridium citroniae	8.52^{-8} (1.03^{-7})	3.21^{-8} (3.29^{-8})	.799	.927	1.01^{-7} (1.03^{-7})	4.90^{-8} (6.40^{-8})	**.001**	.311
Clostridium sp. KLE 1755	9.04^{-8} (1.55^{-7})	2.80^{-8} (5.72^{-8})	.201	.597	2.40^{-7} (2.70^{-7})	1.62^{-7} (4.46^{-7})	**.035**	.654
Clostridiales unclassified CAG01017	0.00 (0.00)	7.73^{-8} (1.25^{-7})	.075	.592	1.17^{-8} (2.20^{-8})	4.98^{-8} (1.28^{-7})	**.049**	.654
Clostridiales unclassified CAG01281	2.42^{-8} (8.05^{-8})	1.57^{-8} (3.90^{-8})	**.006**	.592	4.44^{-10} (1.26^{-9})	1.33^{-7} (4.39^{-7})	.087	.654
Roseburia intestinalis CAG00291	5.09^{-6} (8.80^{-6})	4.71^{-6} (8.35^{-6})	**.028**	.592	2.98^{-6} (6.09^{-6})	6.39^{-7} (1.37^{-6})	.300	.726
Roseburia intestinalis CAG01369	4.94^{-6} (8.59^{-6})	4.42^{-6} (7.70^{-6})	**.032**	.592	2.90^{-6} (5.94^{-6})	5.92^{-7} (1.27^{-6})	.307	.726
Roseburia unclassified CAG00869	7.95^{-8} (1.50^{-7})	5.65^{-8} (6.71^{-8})	.649	.871	4.14^{-8} (8.93^{-8})	1.45^{-7} (2.47^{-7})	**.043**	.654
Flavonifractor sp. 2789STDY5834895	1.40^{-7} (1.55^{-7})	1.52^{-7} (1.71^{-7})	**.018**	.592	2.44^{-7} (5.96^{-7})	4.12^{-7} (5.54^{-7})	.148	.654
Prevotella unclassified CAG00517	5.62^{-8} (2.03^{-7})	3.24^{-8} (1.03^{-7})	**.018**	.592	0.00 (0.00)	1.37^{-6} (4.53^{-6})	.335	.726
Prevotella sp. CAG:520	8.29^{-7} (2.99^{-6})	4.38^{-7} (1.39^{-6})	**.018**	.592	0.00 (0.00)	6.59^{-7} (2.19^{-6})	.148	.654
Eubacterium ventriosum	3.01^{-7} (5.45^{-7})	4.69^{-8} (7.85^{-8})	**.021**	.592	3.74^{-8} (1.01^{-7})	3.86^{-7} (5.64^{-7})	**.043**	.654
Eubacterium hallii	2.02^{-7} (2.57^{-7})	1.66^{-7} (1.62^{-7})	.369	.694	5.35^{-8} (6.15^{-8})	1.73^{-7} (1.57^{-7})	**.036**	.654
Catenibacterium mitsuokai	6.12^{-9} (2.21^{-8})	3.45^{-7} (1.09^{-6})	**.024**	.592	1.25^{-7} (3.53^{-7})	0.00 (0.00)	.311	.726
Barnesiella intestinihominis	3.49^{-6} (5.64^{-6})	1.99^{-6} (2.93^{-6})	**.024**	.592	2.73^{-6} (3.36^{-6})	3.97^{-6} (5.50^{-6})	.638	.862
Firmicutes unclassified CAG00808	9.75^{-8} (2.04^{-7})	1.62^{-8} (4.34^{-8})	.886	.958	2.63^{-8} (3.74^{-8})	4.77^{-8} (1.01^{-7})	**.012**	.654
Firmicutes bacterium CAG:194	0.00 (0.00)	2.02^{-7} (4.02^{-7})	**.036**	.592	0.00 (0.00)	4.25^{-7} (1.41^{-6})	.402	.729
Bacteroides xylanisolvens	2.57^{-6} (6.30^{-6})	1.66^{-6} (2.11^{-6})	.481	.771	1.43^{-5} (2.43^{-5})	2.58^{-6} (4.99^{-6})	**.009**	.563
Bacteroides cellulosilyticus	1.46^{-7} (3.71^{-7})	1.59^{-8} (3.06^{-8})	**.038**	.592	6.14^{-8} (1.74^{-7})	5.69^{-7} (1.10^{-6})	.247	.706
Parabacteroides distasonis	7.40^{-6} (1.61^{-5})	1.15^{-6} (9.61^{-7})	.798	.927	3.99^{-6} (3.84^{-6})	3.25^{-6} (3.22^{-6})	**.007**	.563
Candidatus gastranaerophilales bacterium HUM_2	1.16^{-6} (2.86^{-6})	2.07^{-7} (6.55^{-7})	**.032**	.592	5.99^{-7} (1.69^{-6})	6.49^{-7} (2.11^{-6})	.219	.693
Coprobacter secundus	2.03^{-8} (4.44^{-8})	3.65^{-8} (7.37^{-8})	**.046**	.592	1.80^{-7} (3.06^{-7})	2.63^{-8} (8.74^{-8})	.195	.682
Coprobacter fastidiosus	5.85^{-8} (1.37^{-7})	9.51^{-8} (1.95^{-7})	.951	.975	3.04^{-9} (6.17^{-9})	2.57^{-7} (4.49^{-7})	**.027**	.654
Dorea longicatena 1	3.61^{-7} (5.35^{-7})	6.77^{-7} (9.24^{-7})	.634	.860	1.19^{-7} (7.84^{-8})	5.72^{-7} (5.70^{-7})	**.001**	.311
Dorea longicatena 2 CAG00962	2.61^{-7} (6.72^{-7})	8.13^{-8} (1.16^{-7})	**.009**	.592	3.93^{-8} (5.78^{-8})	1.27^{-7} (3.23^{-7})	.353	.727
Dorea formicigenerans	3.03^{-7} (2.85^{-7})	3.49^{-7} (2.13^{-7})	.512	.785	1.00^{-7} (6.40^{-8})	2.02^{-7} (1.86^{-7})	**.005**	.453
Dorea sp. CAG:105	1.21^{-8} (1.92^{-8})	2.66^{-8} (3.73^{-8})	.924	.973	1.12^{-8} (1.60^{-8})	2.13^{-8} (2.16^{-8})	**.021**	.654
Hungatella hathewayi 2 CAG00015	2.50^{-8} (2.60^{-8})	3.83^{-9} (9.37^{-9})	**.052**	.592	2.56^{-8} (3.91^{-8})	9.46^{-9} (1.22^{-8})	**.021**	.654

Supplementary Table 4. Continued

Genus or species	UC				CD			
	Low FODMAP diet (n = 13)	Sham diet (n = 11)	*P*	*Q*-value	Low FODMAP diet (n = 8)	Sham diet (n = 11)	*P*	*Q*-value
Blautia unclassified CAG00235	1.74^{-7} (4.60^{-7})	9.77^{-9} (2.87^{-8})	.108	.592	8.91^{-10} (2.52^{-9})	5.31^{-8} (9.61^{-8})	**.024**	.654
Anaerostipes hadrus	1.80^{-6} (5.47^{-8})	3.92^{-7} (3.28^{-7})	.209	.597	1.48^{-7} (1.19^{-7})	6.37^{-7} (6.58^{-7})	**.005**	.453
Haemophilus parainfluenzae CAG00950	9.40^{-8} (1.32^{-7})	4.06^{-8} (7.41^{-8})	.715	.901	1.24^{-7} (2.52^{-7})	2.49^{-8} (5.14^{-8})	**.002**	.311
Haemophilus parainfluenzae CAG01056	6.50^{-7} (1.08^{-6})	3.58^{-7} (6.93^{-7})	.542	.798	9.61^{-7} (2.14^{-6})	1.94^{-7} (3.77^{-7})	**.033**	.654
Streptococcus thermophilus	4.93^{-8} (6.58^{-8})	1.59^{-8} (2.31^{-8})	.245	.628	2.81^{-9} (7.95^{-9})	6.21^{-8} (1.48^{-7})	**.019**	.654
Massiliomicrobiota CAG00816	5.65^{-8} (1.75^{-7})	3.22^{-9} (7.35^{-9})	.318	.660	0.00 (0.00)	8.64^{-9} (1.45^{-8})	**.025**	.654
Fusicatenibacter saccharivorans	1.26^{-6} (1.29^{-6})	1.00^{-6} (1.07^{-6})	.704	.901	4.67^{-7} (2.90^{-7})	1.76^{-6} (1.73^{-6})	**.027**	.654
Eisenbergiella tayi	1.24^{-7} (3.02^{-7})	7.64^{-9} (1.36^{-8})	.075	.592	2.28^{-7} (4.92^{-7})	1.69^{-8} (4.08^{-8})	**.019**	.654
Adlercreutzia equolifaciens	1.75^{-7} (2.18^{-7})	6.69^{-8} (7.42^{-8})	.471	.762	2.76^{-8} (2.74^{-8})	5.54^{-8} (6.39^{-8})	**.003**	.447
Alistipes onderdonkii	9.11^{-7} (1.25^{-6})	4.06^{-7} (1.06^{-6})	**.015**	.592	1.29^{-5} (2.68^{-5})	2.18^{-6} (4.41^{-6})	.336	.726
Intestinimonas massiliensis	1.08^{-7} (2.57^{-7})	1.71^{-9} (5.42^{-9})	**.023**	.592	2.17^{-8} (3.66^{-8})	1.11^{-7} (2.41^{-7})	.128	.654
Lachnoclostridium unclassified CAG00764	3.36^{-7} (6.64^{-7})	5.11^{-8} (9.28^{-8})	**.022**	.592	1.37^{-7} (2.56^{-7})	2.17^{-7} (3.47^{-7})	.307	.726
Unclassified CAG00420	2.69^{-8} (5.38^{-8})	7.54^{-8} (1.63^{-7})	**.024**	.592	1.43^{-8} (2.85^{-8})	5.85^{-8} (1.17^{-7})	.128	.654

NOTE. Data are presented as mean (SD) relative abundance and were compared between groups adjusted for baseline abundance and end of trial stool consistency. None of these species were significantly different between diet groups after FDR correction.

Supplementary Table 5. Total and Individual SCFA Concentrations in the ITT and PP Analysis

	ITT analysis			PP analysis		
	Low FODMAP diet (n = 27)	Sham diet (n = 25)	*P*	Low FODMAP diet (n = 21)	Sham diet (n = 22)	*P*
Total SCFA	398 (192)	556 (245)	.080	366 (174)	536 (251)	**.049**
Acetate	232 (117)	323 (138)	.073	213 (109)	313 (140)	**.044**
Butyrate	67 (42)	92 (58)	.102	62 (40)	86 (60)	.094
Propionate	76 (41)	108 (71)	.190	69 (36)	104 (71)	.138
Valerate	7 (5)	11 (8)	.169	7 (4)	10 (8)	.164
Isobutyrate	7 (3)	9 (6)	.142	6 (3)	9 (6)	.084
Isovalerate	10 (5)	13 (9)	.468	9 (4)	13 (9)	.304
pH	6.7 (0.6)	6.4 (0.6)	.329	6.7 (0.6)	6.5 (0.6)	.409

NOTE. Data are presented as estimated marginal mean (SEM) and were compared between groups using an analysis of covariance with baseline values as a covariate.

Supplementary Table 6. T-cell Subset Analysis: Proportion of Each Population Expressing $\alpha4\beta7+$ and Absolute Number of $\alpha4\beta7+$ Cells at End of Trial

	Low FODMAP diet (n = 27)	Sham diet (n = 23)	*P*
Naïve CD4+			
Proportion (%)	67.1 (2.9)	74.0 (3.2)	.116
Absolute	333,815 (4024)	279,761 (4466)	.377
Effector/memory CD4+			
Proportion (%)	38.7 (1.2)	41.1 (1.3)	.164
Absolute	166,034 (1634)	164,934 (1821)	.965
Naïve CD8+			
Proportion (%)	68.9 (2.5)	74.6 (2.7)	.135
Absolute	225,275 (2486)	172,076 (2759)	.163
Effector/memory CD8+			
Proportion (%)	63.6 (2.3)	69.9 (2.3)	.054
Absolute	81,845 (8812)	80,040 (9803)	.894
Vδ2+			
Proportion (%)	71.6 (2.0)	79.1 (2.2)	**.017**
Absolute	30,535 (3897)	31,140 (4419)	.377

NOTE. Data are presented as estimated marginal mean (SEM) and were compared between groups using an analysis of covariance with baseline values as a covariate.