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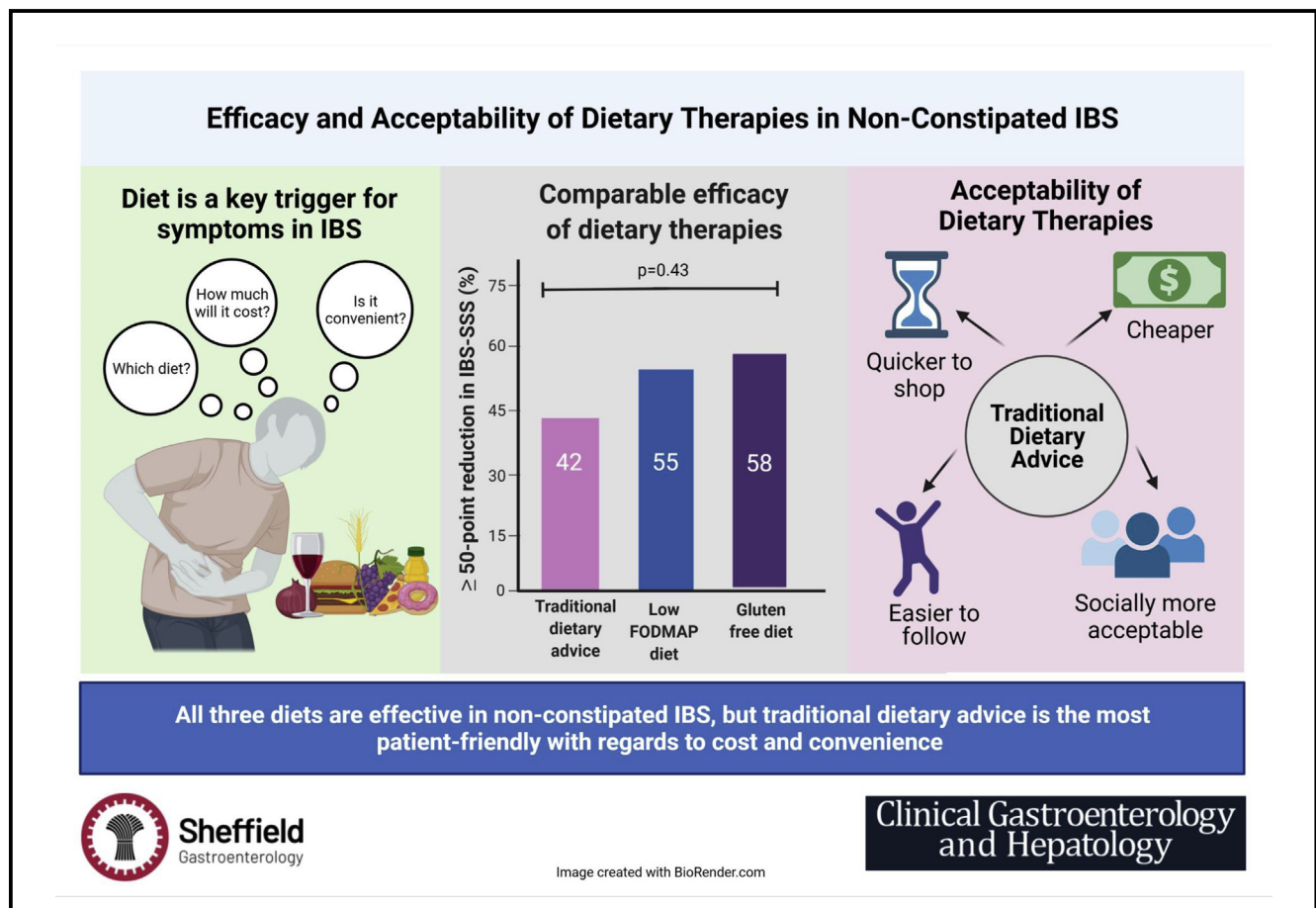
# Efficacy and Acceptability of Dietary Therapies in Non-Constipated Irritable Bowel Syndrome: A Randomized Trial of Traditional Dietary Advice, the Low FODMAP Diet, and the Gluten-Free Diet

Anupam Rej,<sup>\*,‡</sup> David S. Sanders,<sup>\*,‡</sup> Christian C. Shaw,<sup>\*</sup> Rachel Buckle,<sup>\*</sup> Nick Trott,<sup>\*</sup> Anurag Agrawal,<sup>§</sup> and Imran Aziz<sup>\*,‡</sup>

<sup>\*</sup>Academic Unit of Gastroenterology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom;

<sup>‡</sup>Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom; and

<sup>§</sup>Doncaster and Bassetlaw Hospitals NHS Trust, Doncaster, United Kingdom



**Abbreviations used in this paper:** COVID-19, coronavirus disease 2019; DI, dybiosis index; DRV, dietary reference value; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides; and polyols, GFD; gluten-free diet, GI; gastrointestinal, IBS; irritable bowel syndrome, IBS-D; IBS-diarrhea, IBS-M; IBS-mixed type, IBS-SSS; IBS symptom severity score, LFD; diet low in fermentable oligosaccharides, disaccharides; monosaccharides, and polyols; QOL, quality of life; TDA, traditional dietary advice.

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**BACKGROUND & AIMS:** Various diets are proposed as first-line therapies for non-constipated irritable bowel syndrome (IBS) despite insufficient or low-quality evidence. We performed a randomized trial comparing traditional dietary advice (TDA) against the low FODMAP diet (LFD) and gluten-free diet (GFD).

**METHODS:** Patients with Rome IV–defined non-constipated IBS were randomized to TDA, LFD, or GFD (the latter allowing for minute gluten cross-contamination). The primary end point was clinical response after 4 weeks of dietary intervention, as defined by  $\geq 50$ -point reduction in IBS symptom severity score (IBS-SSS). Secondary end points included (1) changes in individual IBS-SSS items within clinical responders, (2) acceptability and food-related quality of life with dietary therapy, (3) changes in nutritional intake, (4) alterations in stool dysbiosis index, and (5) baseline factors associated with clinical response.

**RESULTS:** The primary end point of  $\geq 50$ -point reduction in IBS-SSS was met by 42% ( $n = 14/33$ ) undertaking TDA, 55% ( $n = 18/33$ ) for LFD, and 58% ( $n = 19/33$ ) for GFD ( $P = .43$ ). Responders had similar improvements in IBS-SSS items regardless of their allocated diet. Individuals found TDA cheaper ( $P < .01$ ), less time-consuming to shop ( $P < .01$ ), and easier to follow when eating out ( $P = .03$ ) than the GFD and LFD. TDA was also easier to incorporate into daily life than the LFD ( $P = .02$ ). Overall reductions in micronutrient and macronutrient intake did not significantly differ across the diets. However, the LFD group had the greatest reduction in total FODMAP content (27.7 g/day before intervention to 7.6 g/day at week 4) compared with the GFD (27.4 g/day to 22.4 g/day) and TDA (24.9 g/day to 15.2 g/day) ( $P < .01$ ). Alterations in stool dysbiosis index were similar across the diets, with 22%–29% showing reduced dysbiosis, 35%–39% no change, and 35%–40% increased dysbiosis ( $P = .99$ ). Baseline clinical characteristics and stool dysbiosis index did not predict response to dietary therapy.

**CONCLUSIONS:** TDA, LFD, and GFD are effective approaches in non-constipated IBS, but TDA is the most patient-friendly in terms of cost and convenience. We recommend TDA as the first-choice dietary therapy in non-constipated IBS, with LFD and GFD reserved according to specific patient preferences and specialist dietetic input. Clinicaltrials.gov: NCT04072991.

*Keywords:* Irritable Bowel Syndrome; Diet; Acceptability; Nutrition; Microbiome.

Irritable bowel syndrome (IBS) is a common functional bowel disorder characterized by chronic abdominal pain, bloating, and altered bowel habit.<sup>1</sup> Dietary therapies are frequently recommended in IBS, because more than 80% of individuals report food-related symptoms,<sup>2</sup> with almost 63% wanting to know which food(s) they should avoid.<sup>3</sup>

The last decade has seen 3 diets popularized for non-constipated IBS, which are (1) traditional dietary advice (TDA), (2) a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) (LFD), and (3) a gluten-free diet (GFD).<sup>4</sup> Of these, TDA is the first-line dietary therapy within the United Kingdom and is based on guidance provided by the National Institute for Health and Care Excellence and the British Dietetic Association.<sup>5–7</sup> Its principles include adopting healthy, sensible eating patterns such as having regular meals, never eating too little/too much, maintaining adequate hydration, and reducing the intake of (1) alcohol/caffeine/fizzy drinks, (2) fatty/spicy/processed foods, (3) fresh fruit to a maximum of 3 per day, (4) fiber and other commonly consumed gas-producing foods (eg, beans, bread, sweeteners, etc), and (5) addressing any perceived food intolerances (eg, dairy). The LFD is the second-line dietary therapy for IBS within the United

Kingdom,<sup>5–7</sup> although in North America it is first-line.<sup>8,9</sup> FODMAPs are short-chain fermentable carbohydrates found in a variety of fruits, vegetables, dairy products, artificial sweeteners, and wheat. They increase small intestinal water volume and colonic gas production that, in those with visceral hypersensitivity, induce gastrointestinal (GI) symptoms.<sup>7</sup> The LFD initially eliminates all FODMAPs for 4–6 weeks, followed by their gradual reintroduction and personalization. Finally, taking a GFD without celiac disease has become a global phenomenon, with  $\sim 10\%$  of the population reporting gluten-based products to provoke intestinal symptoms compatible with IBS.<sup>10</sup> The mechanism for symptom improvement on a GFD are extensively debated but appear, in the main, not to be via the removal of gluten per se but rather through reducing fructan content (a FODMAP) due to wheat exclusion.<sup>11</sup>

Although heavily promoted, these diets are limited in evidence.<sup>7,12</sup> Recommendations for TDA are mainly based on clinical experience and the potential mechanisms by which these foods may induce symptoms, as opposed to randomized controlled trials.<sup>6</sup> With regard to a LFD, historical and contemporary reviews report an efficacy approaching  $\sim 75\%$ ,<sup>13,14</sup> although a 2018 systematic review and meta-analysis of randomized

controlled trials concluded there to be low-quality evidence, mainly because of small sample sizes and significant heterogeneity between studies.<sup>12</sup> Interestingly, the few studies that compared the LFD with TDA demonstrated the least magnitude of effect,<sup>12</sup> with a response rate of 40%–50%, although some debated whether the LFD was (sub)optimally delivered and its efficacy underestimated.<sup>15–17</sup> Additional studies have since been performed,<sup>18–20</sup> with a 2021 network meta-analysis ranking the LFD first among the dietary therapies for IBS, deeming it superior to TDA.<sup>21</sup> Yet, trials of TDA were limited to 5 studies, had far fewer participants compared with a LFD, and some modified its recommended instructions ([Supplementary Table 1](#)).<sup>16–21</sup> For example, 4 of 5 studies did not advise patients to reduce commonly consumed gas-producing foods,<sup>17–20</sup> which contradicts the TDA concept and conceivably underestimates its efficacy. Although it may be argued that TDA overlaps with the LFD, they are appreciable differences in that the former advises reducing commonly consumed gas-producing foods, whereas the latter initially eliminates them all. A GFD in IBS has also come under scrutiny because despite reports of ~70% efficacy, a systematic review and meta-analysis identified only 2 randomized trials and concluded insufficient evidence.<sup>4,12</sup>

In addition, some previous IBS dietary trials have been feeding studies that, despite being a powerful proof-of-concept tool,<sup>12</sup> do not address the challenges placed on patients to incorporate the diets into their everyday personal and social life. This may be of relevance with the conceivably more complex LFD and GFD, which also require specialist dietetic input before implementation and incur substantial pressures on publicly funded healthcare services.<sup>7</sup> Concerns have also been raised that restrictive diets may induce potentially detrimental nutritional and stool microbial changes.<sup>4</sup>

In summary, there is no pragmatic head-to-head trial comparing the efficacy and acceptability of the LFD and GFD against TDA. We hypothesized that the LFD and GFD will be superior to TDA in improving IBS symptoms and performed a randomized trial to address this. We also investigated the acceptability, nutritional and stool microbial changes associated with these diets. Finally, we evaluated whether baseline factors predict a response to dietary intervention, because this could lead to future provision of personalized care.

## Methods

### *Participants and Setting*

All authors had access to the study data and reviewed and approved the final manuscript. Patients were recruited via 2 secondary care centers in the United Kingdom. The inclusion criteria were adults aged  $\geq 18$  years with Rome IV IBS-diarrhea (IBS-D) or mixed-type (IBS-M), and an IBS-symptom severity score (IBS-SSS)

## What You Need to Know

### Background

Dietary therapies are popular for the management of irritable bowel syndrome (IBS), yet data on their comparative efficacy and acceptability are limited.

### Findings

Traditional dietary advice is effective like the low FODMAP and gluten-free diet but is more patient-friendly with regard to cost, time to shop, and ease of implementation.

### Implications for patient care

Traditional dietary advice should be considered the first-choice dietary therapy in IBS, with the low FODMAP and gluten-free diet reserved according to specific patient preferences and with specialist dietetic counseling.

of  $>75$ . The exclusion criteria are in the [Supplementary Methods](#).

### *Randomization*

Patients were allocated TDA, the LFD, or GFD (the latter not being strict as in celiac disease, because gluten cross-contamination was allowed, eg, sharing the same household toaster). Individuals were block-randomized into groups of up to 5, with diets given in a 1:1:1 ratio. The randomization was computer-generated and performed by an individual not involved in recruitment or treatment. Participants were seen face-to-face by specialist dietitians where they were educated on their allocated diet via a standardized 45- to 60-minute presentation, including time for questions, followed by appropriate dietary information sheets. However, after the onset of coronavirus disease 2019 (COVID-19), delivery of dietetic advice was transferred to a web-based live virtual consult, with the same information provided as with face-to-face. Participants commenced their allocated diet for 4 weeks, with outcomes at week 4 compared with baseline.

### *Questionnaires*

Participants provided baseline demographic data. Their socioeconomic status was also determined by using the Index of Multiple Deprivation 2019 scale, because this may contribute toward an individual's biopsychosocial model and their response to dietary therapy.

The following questionnaires were completed before and after dietary intervention, with further information provided in [Supplementary Material](#).

- (1) IBS-SSS,

- (2) Hospital Anxiety and Depression Scale,
- (3) Patient health questionnaire-12 non-GI somatic symptoms scale,
- (4) IBS quality of life (QOL) questionnaire,
- (5) Acceptability of dietary restriction questionnaire,
- (6) Food-related QOL questionnaire, and
- (7) Comprehensive Nutrition Assessment Questionnaire (CNAQ).

### Stool Samples

Participants provided stool samples before and after dietary intervention. However, this process was temporarily suspended at the start of COVID-19 and resumed once allowed. Hence, stool samples were collected in around half of cases. Data were analyzed using the GAmmap Dysbiosis Test, with bacterial profiles assigned a dysbiosis index (DI) on a scale from 0 to 5, with >2 indicating a bacteria composition differing from a healthy normobiotic reference range and, as such, considered dysbiotic. Further information regarding stool sample analysis is in [Supplementary Material](#).

### End Points

The primary end point was % clinical responders after 4 weeks of dietary intervention, as defined by  $\geq 50$ -point reduction in IBS-SSS, which has been shown to represent a clinically significant improvement. Secondary end points included (1) changes in individual IBS-SSS items in those with a clinical response, (2) changes in anxiety, depression, somatization, QOL, nutritional intake, gut microbiota, and (3) acceptability and food-related QOL associated with dietary therapy. An assessment was also made on whether baseline factors (age, gender, Index of Multiple Deprivation, mood, somatization, stool DI) might be associated with clinical response to dietary therapy.

### Sample Size and Statistical Analysis

The sample size calculation considered the aforementioned ambiguities regarding the true efficacy of a LFD or GFD, with some groups reporting  $\sim 75\%$  response,<sup>13,14,22,23</sup> and questioning the lower response rates from randomized trials.<sup>15</sup> Furthermore, detecting a large effect size might be desirable if demanding diets (ie, LFD/GFD) were to be considered first choice over the relatively straightforward TDA. Assuming a response rate of 75% with LFD or GFD and 40% with TDA, 31 subjects per arm were required to detect a 35% difference with 80% power at  $\alpha = 0.05$ . To accommodate 10% dropout rate, we aimed for 33 individuals per arm. Of note, the effect size is comparable with previous studies<sup>16,17</sup> and those published recently.<sup>18–20</sup>

Full details on statistical analyses are in [Supplementary Material](#). The  $P$  value was significant at  $<.05$ , with post hoc Bonferroni corrections performed as required.

## Results

Of 114 participants recruited, 101 commenced dietary intervention (TDA = 35, LFD = 33, GFD = 33), with 2 excluded as lost to follow-up. A total of 99 participants, 33 per arm, completed the study ([Supplementary Figure 1](#)). There was no difference in baseline variables across groups ([Supplementary Table 2](#)). The mean age was 37 years, with 71% female, 88% white, 75% IBS-D, and 25% IBS-M. The mean baseline IBS-SSS was 301, with 9% having mild IBS, 47% moderate IBS, and 45% severe IBS ( $P = .5$  across groups).

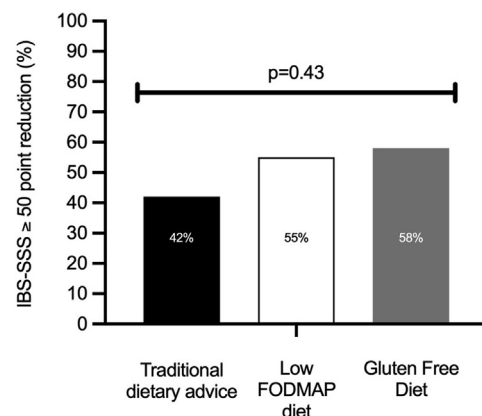
### Clinical Response

The primary end point of  $\geq 50$ -point reduction in IBS-SSS was met by 42% ( $n = 14/33$ ) taking TDA, 55% with LFD ( $n = 18/33$ ), and 58% with GFD ( $n = 19/33$ ), with no significant difference across groups ( $P = .43$ ) ([Figure 1](#)).

Of those who experienced  $\geq 50$ -point reduction in IBS-SSS, there were significant within-group improvements in individual IBS-SSS items. This was seen with each dietary therapy but with no significant difference across groups ([Table 1](#)).

A  $\geq 50$ -point reduction in IBS-SSS was seen in 52% ( $n = 15/29$ ) receiving face-to-face consult vs 51% ( $n = 36/70$ ) receiving live virtual consult ( $P = .98$ ). This was seen to a similar extent irrespective of the allocated dietary therapy (data not shown).

A  $\geq 50$ -point reduction in IBS-SSS was seen in 54% ( $n = 40/74$ ) with IBS-D vs 44% ( $n = 11/25$ ) with IBS-M, with no difference between groups ( $P = .38$ ). There was no statistical difference in response rates between IBS-D vs IBS-M on the basis of a particular dietary therapy (data not shown).



**Figure 1.** Response rate to dietary therapies.



**Table 1.** Change in IBS-SSS and Its Individual Items in Patients Responding to Dietary Therapy (n = 51 of 99)

IBS-SSS and its individual items, mean (standard deviation)	Intervention												Difference in reduction across groups, P value
	TDA (n = 14)			LFD (n = 18)			GFD (n = 19)						
	Baseline	Week 4	Within-group change <sup>a</sup>	Baseline	Week 4	Within-group change <sup>a</sup>	Baseline	Week 4	Within-group change <sup>a</sup>	Baseline	Week 4	Within-group change <sup>a</sup>	
IBS-SSS	330 (74)	199 (93)	131	311 (80)	148 (87)	163	299 (73)	180 (89)	119				.13
Abdominal pain severity	51 (22)	28 (30)	23	55 (23)	18 (17)	37	52 (22)	25 (21)	27				.11
No. of days in pain every 10 days	6.1 (2.5)	3.5 (3.2)	2.6	6.0 (2.9)	3.1 (2.3)	2.9	6.4 (1.8)	3.7 (2.6)	2.7				.93
Abdominal distention severity	63 (24)	28 (26)	35	54 (32)	22 (23)	32	49 (24)	21 (22)	28				.61
Satisfaction with bowel habits	78 (19)	58 (30)	20	75 (25)	44 (32)	31	71 (24)	52 (28)	19				.50
Interference with life in general	76 (15)	50 (26)	26	67 (22)	33 (28)	34	63 (22)	44 (32)	19				.17

NOTE. Values presented as mean (standard deviation).

<sup>a</sup>Significant within-group reductions for all IBS-SSS items.

### Impact on Mood, Somatization, and IBS-QOL

Individuals allocated a LFD had a significant improvement in depression compared with TDA. Changes in anxiety, somatization, and IBS QOL did not differ across groups, except for the LFD having a significant improvement in dysphoria compared with TDA and GFD (Supplementary Table 3).

### Acceptability of Dietary Restriction and Food-Related QOL

Individuals found TDA cheaper ( $P < .01$ ), less time-consuming to shop ( $P < .01$ ), and easier to follow when eating out at family and friends ( $P = .03$ ) compared with a GFD and LFD. Individuals found TDA and GFD easier to incorporate into their life than the LFD ( $P = .02$ ) (Table 2).

The proportions of individuals who would consider continuing the diets were 70% (n = 23) for TDA, 67% (n = 22) for LFD, and 61% (n = 20) for GFD, with no difference across groups ( $P = .73$ ).

### Nutritional Intake and FODMAP Composition

Although macronutrients and micronutrients reduced within each dietary group, there was no significant difference across groups besides a trend toward more fiber reduction on the LFD compared with the GFD and TDA ( $P = .06$ ) (Table 3).

The proportion of individuals meeting recommended dietary reference values (DRVs) for macronutrients did not change before to after intervention for any of the diets. However, DRVs for the micronutrients of potassium and iron were significantly reduced with TDA, whereas thiamine and magnesium were significantly reduced with the LFD and GFD. The majority of individuals across all 3 diets failed to meet DRVs for total energy intake both before and after intervention (Supplementary Table 4).

Significant within-group reduction in total FODMAP intake occurred with all 3 diets (Table 4). However, the greatest reduction was with a LFD (27.7 g/day before intervention to 7.6 g/day at week 4) compared with TDA (24.9 g/day to 15.2 g/day) and GFD (27.4 g/day to 22.4 g/day) ( $P < .01$ ).

As expected, the LFD led to significant reductions in each individual FODMAP component, whereas with TDA it was for fructo-oligosaccharides, lactose, and mannitol, and with the GFD it was for fructo- and galacto- oligosaccharides. The LFD led to a significantly greater reduction in fructo-oligosaccharides, galacto-oligosaccharides, and mannitol compared with TDA and a significantly greater reduction in lactose, excess fructose, and mannitol compared with the GFD (Table 4).

**Table 2.** Acceptability of Dietary Restriction and Food-Related QOL

	Agree, n (%)			Neutral, n (%)			Disagree, n (%)			Comparison across groups <i>p</i> -value
	TDA	LFD	GFD	TDA	LFD	GFD	TDA	LFD	GFD	
Acceptability of dietary restriction										
I find it easy to buy suitable foods for my current diet at my normal supermarkets or shops.	19 (58)	12 (36)	18 (55)	13 (39)	13 (39)	11 (33)	1 (3)	8 (24)	4 (12)	.1
I am able to buy foods suitable for my current diet at my normal supermarkets or shops.	23 (70)	18 (55)	26 (79)	7 (21)	11 (33)	6 (18)	3 (9)	4 (12)	1 (3)	.3
I use high street/online specialty shops (eg, health food shops) to buy food for my current diets.	8 (24)	3 (9)	9 (27)	7 (21)	7 (21)	7 (21)	18 (55)	23 (70)	17 (52)	.4
It takes extra time to shop for my current diet.	13 (39)	26 (79)	23 (70)	7 (21)	4 (12)	8 (24)	13 (39)	3 (9)	2 (6)	<.01 <sup>a</sup>
I find food labelling is adequate to allow me to confidently choose suitable foods.	18 (55)	20 (61)	28 (85)	13 (39)	9 (27)	3 (9)	2 (6)	4 (12)	2 (6)	.04
The cost of my current diet is more expensive.	16 (49)	27 (82)	27 (82)	8 (24)	3 (9)	6 (18)	9 (27)	3 (9)	0 (0)	<.01 <sup>a</sup>
Does eating out at restaurants make it more difficult for you to follow your current diet?	19 (58)	20 (61)	19 (58)	9 (27)	12 (36)	11 (33)	5 (15)	1 (3)	3 (9)	.5
Does eating out at friends/families make it more difficult for you to follow your current diet?	17 (52)	22 (67)	22 (67)	7 (21)	10 (30)	9 (27)	9 (27)	1 (3)	2 (6)	.03 <sup>a</sup>
Does travel (overseas/United Kingdom) make it more difficult for you to follow your current diet?	18 (55)	15 (46)	13 (39)	11 (33)	16 (49)	18 (55)	4 (12)	2 (6)	2 (6)	.5
Overall, I find my current diet tasty and enjoyable.	17 (52)	14 (42)	13 (39)	11 (33)	9 (27)	18 (55)	5 (15)	10 (30)	2 (6)	.04
I can incorporate my current diet easily into my life.	18 (55)	11 (33)	15 (46)	13 (39)	11 (33)	15 (46)	2 (6)	11 (33)	3 (9)	.02 <sup>b</sup>
My current dietary needs have created stress with my family/friends.	3 (9)	8 (24)	8 (24)	13 (39)	11 (33)	10 (30)	17 (52)	14 (42)	15 (46)	.5
Food-related QOL										
Food and meals are positive elements of my life.	17 (52)	17 (52)	22 (67)	13 (39)	6 (18)	8 (24)	3 (9)	10 (30)	3 (9)	.05
I am generally pleased with my food.	22 (67)	15 (46)	17 (52)	8 (24)	9 (27)	14 (42)	3 (9)	9 (27)	2 (6)	.05
My life in relation to food and meals is close to my ideal.	6 (18)	7 (21)	7 (21)	14 (42)	11 (33)	19 (58)	13 (39)	15 (46)	7 (21)	.3
With regard to food, the conditions of my life are excellent.	4 (12)	6 (18)	9 (27)	18 (55)	12 (36)	17 (52)	11 (33)	15 (46)	7 (21)	.2
Food and meals give me satisfaction in daily life.	20 (61)	15 (46)	18 (55)	9 (27)	6 (18)	10 (30)	4 (12)	12 (36)	5 (15)	.1
I wish my meals were much more pleasant part of my life.	11 (33)	20 (61)	13 (39)	11 (33)	7 (21)	13 (39)	11 (33)	6 (18)	7 (21)	.2
When I think of my next meal, I only see problems, obstacles, and disappointments.	4 (12)	11 (33)	7 (21)	11 (33)	13 (39)	13 (39)	18 (55)	9 (27)	13 (39)	.2

<sup>a</sup>Statistically significant difference between TDA vs LFD and GFD on post hoc analysis.<sup>b</sup>Statistically significant difference between LFD vs TDA and GFD on post hoc analysis.

**Table 3.** Nutritional Intake at Baseline and Week 4 of Dietary Therapy

Nutritional parameter	Intervention						Difference in reduction across groups, <i>P</i> value
	TDA		LFD		GFD		
	Baseline	Week 4	Baseline	Week 4	Baseline	Week 4	
Energy, <i>kcal/d</i>	2373 (1774–2923)	1861 (1579–2411)	2338 (1574–2764)	1738 (1210–2231)	2366 (2030–2928)	1958 (1406–2770)	.63
Protein, <i>g/d</i>	104.2 (81.6–160.4)	90.9 (65.6–108.6)	97.1 (74.1–118.6)	80.4 (51.6–95.7)	99.7 (74.4–132.6)	79.1 (61.5–105.3)	.52
Carbohydrate, <i>g/d</i>	268 (224–342)	222 (203–320)	277 (211–357)	223 (141–277)	307 (231–375)	227 (174–306)	.55
Fat, <i>g/d</i>	86.8 (57.9–112.2)	65.3 (44.5–87.8)	82.3 (56.9–114.9)	64.6 (43.5–95.2)	86.1 (71.0–115.8)	77.9 (49.3–113.0)	.66
Dietary fiber, <i>g/d</i>	32.6 (27.4–40.7)	28.5 (21.4–35.4)	23.5 (16.8–44.1)	18.7 (14.3–31.7)	32.7 (23.4–39.3)	25.9 (21.1–35.0)	.06
Folate, $\mu\text{g/d}$	449 (351–583)	353 (273–496)	362 (219–592)	291 (175–407)	392 (311–524)	335 (254–496)	.22
Thiamine, <i>mg/d</i>	1.70 (1.38–2.73)	1.40 (1.10–1.73)	1.40 (1.00–2.40)	1.00 (0.60–1.45)	1.50 (1.30–2.55)	1.10 (0.80–1.70)	.13
Riboflavin, <i>mg/d</i>	2.50 (1.70–4.25)	2.00 (1.20–2.63)	1.90 (1.43–3.28)	1.65 (1.13–2.53)	2.10 (1.80–3.70)	2.00 (1.30–2.90)	.12
Niacin, <i>mg/d</i>	24.0 (16.1–30.3)	19.6 (16.6–23.9)	19.1 (13.3–25.3)	14.8 (11.5–20.9)	20.2 (18.6–27.7)	17.7 (15.1–23.2)	.72
Vitamin C, <i>mg/d</i>	185 (143–280)	172 (115–250)	111 (78–251)	94 (73–213)	163 (124–244)	150 (117–204)	.16
Sodium, <i>mg/d</i>	2772 (1695–3204)	1947 (1516–2485)	2220 (1641–2915)	1761 (1372–2642)	2424 (1980–3217)	1910 (1446–2902)	.97
Potassium, <i>mg/d</i>	4394 (3739–5620)	3704 (2967–4807)	4042 (2819–5077)	3119 (2097–3813)	4039 (3469–5370)	3518 (2582–4577)	.50
Magnesium, <i>mg/d</i>	377 (288–517)	315 (252–423)	324 (238–440)	247 (169–333)	347 (292–426)	298 (234–379)	.36
Calcium, <i>mg/d</i>	1122 (917–2030)	896 (625–1357)	991 (714–2069)	888 (520–1330)	1057 (792–1699)	1049 (605–1510)	.14
Phosphorus, <i>mg/d</i>	1771 (1424–2569)	1476 (1202–1750)	1472 (1146–2111)	1365 (853–1793)	1606 (1200–2382)	1435 (1067–1956)	.41
Iron, <i>mg/d</i>	13.4 (9.4–14.3)	11.5 (9.4–14.3)	11.7 (8.5–15.6)	10.4 (6.5–14.1)	12.7 (10.0–16.0)	10.6 (8.6–13.9)	.70
Zinc, <i>mg/d</i>	11.8 (8.6–14.9)	10.7 (8.3–13.2)	11.0 (8.7–13.3)	11.1 (6.3–12.9)	11.2 (8.7–15.0)	10.9 (7.5–15.0)	.70

Footnote: Values presented as median (IQR).

Significant within-group reductions seen with most macro- and micro- nutrients following dietary intervention, except for zinc (all diets), vitamin C (TDA and GFD), and fibre/folate/riboflavin (GFD)

NOTE. Values presented as median (interquartile range). Significant within-group reductions seen with most macronutrients and micro nutrients after dietary intervention, except for zinc (all diets), vitamin C (TDA and GFD), and fiber/folate/riboflavin (GFD).



**Table 4.** FODMAP Intake at Baseline and Week 4 of Dietary Therapy

FODMAP	Intervention									Difference in change across groups, <i>P</i> value
	TDA			LFD			GFD			
	Baseline	Week 4	Baseline vs Week 4, <i>P</i> value	Baseline	Week 4	Baseline vs. Week 4, <i>P</i> value	Baseline	Week 4	Baseline vs Week 4, <i>P</i> value	
Oligosaccharides										
Fructo-oligosaccharides, <i>g/d</i>	3.8 (2.7–4.7)	2.9 (2.2–3.7)	<.01	3.3 (1.8–6.2)	1.6 (0.8–2.5)	<.01	3.9 (3.0–4.5)	2.4 (1.6–4.0)	<.01	<.01 <sup>a</sup>
Galacto-oligosaccharides, <i>g/d</i>	1.1 (0.8–1.5)	1.1 (0.7–1.3)	.05	1.2 (0.6–2.2)	0.6 (0.3–1.1)	<.01	1.2 (0.9–2.2)	0.9 (0.7–1.6)	.02	<.01 <sup>a</sup>
Disaccharides										
Lactose, <i>g/d</i>	11.7 (4.3–26.4)	4.9 (1.0–15.0)	<.01	12.5 (3.3–24.0)	1.9 (0.5–6.5)	<.01	14.3 (7.0–26.0)	13.0 (4.6–22.0)	.22	.02 <sup>b</sup>
Monosaccharides										
Excess fructose, <i>g/d</i>	5.2 (2.6–7.0)	2.8 (1.7–6.8)	.31	3.5 (2.0–10.4)	1.5 (0.8–3.5)	<.01	4.0 (2.3–6.6)	4.0 (2.2–6.4)	.95	<.01 <sup>b</sup>
Polyols										
Sorbitol, <i>g/d</i>	1.9 (0.7–3.0)	1.4 (0.4–2.8)	.18	1.3 (0.6–2.2)	0.3 (0.1–1.0)	<.01	2.1 (1.1–3.2)	1.9 (0.9–3.4)	.84	.05
Mannitol, <i>g/d</i>	0.8 (0.5–1.1)	0.6 (0.4–1.0)	<.01	0.6 (0.3–0.8)	0.1 (0.0–0.3)	<.01	0.7 (0.4–1.1)	0.6 (0.3–1.1)	.70	<.01 <sup>a,b</sup>
Total FODMAPs, <i>g/d</i>	24.9 (13.8–53.4)	15.2 (9.1–28.0)	<.01	27.7 (13.9–46.3)	7.6 (2.8–13.7)	<.01	27.4	22.4	.03	<.01 <sup>a,b</sup>

NOTE. Values presented as medians (interquartile range).

<sup>a</sup>Statistically significant difference between LFD and TDA on post hoc analysis.

<sup>b</sup>Statistically significant difference between LFD and GFD on post hoc analysis.

## Stool Analysis

A total of 55 paired stool samples were analyzed (TDA = 18, LFD = 17, GFD = 20). Changes in DI did not differ across groups ( $P = .99$ ), with 22%–29% having an improvement, 35%–39% having no change, and 35%–40% having worsening DI (Figure 2). Changes in DI did not differ between responders and non-responders (Supplementary Table 5).

No significant changes in functional bacterial profiles were noted (Supplementary Table 6), with specific alterations in bacterial abundance reported in Supplementary Tables 7–9.

## Factors Associated With Clinical Response

Age, gender, IBS subtype, Index of Multiple Deprivation, somatization, and mood did not predict response to dietary therapies (Supplementary Table 10), and baseline stool DI did not (Supplementary Figure 2).

## Discussion

This is a randomized trial comparing the efficacy and convenience of TDA, LFD, and GFD in non-constipated IBS. The pragmatic study design, whereby the responsibility was left on patients to undertake the diets following appropriate education, means our findings can be generalized. The main results are that the diets did not significantly differ in clinical efficacy, with 42%–58% experiencing a  $\geq 50$ -point reduction in IBS-SSS. Responders had similar improvements in IBS-SSS items regardless of their allocated diet. Individuals found TDA cheaper, less time-consuming to shop, and easier to follow when eating out than the GFD and LFD. It was also easier to implement into everyday life than the LFD. Neither clinical characteristics nor stool DI predicted response to dietary therapy. Finally, the modes of dietary education, either face-to-face or virtual, were equally effective.

Our study has notable strengths. First, it is among the largest studies assessing dietary therapies in IBS.<sup>12</sup> Second, we provided dietary education as per recommended instructions,<sup>5,6</sup> whereas 4 of 5 previous randomized

trials of TDA have been limited to providing a modified or incomplete version.<sup>17–20</sup> This could partly explain TDA being ranked inferior to a LFD in a recent network meta-analysis.<sup>21</sup> Our findings shed further clarity on the efficacy of TDA and are in line with a Swedish randomized trial that provided TDA instructions as per guidance and noted no difference versus the LFD.<sup>16</sup> The added value of our study is its assessment of dietary acceptability, as well as evaluating a GFD, which has become increasingly popular in modern times. Although a recent Italian study demonstrated similar clinical efficacy between the LFD, GFD, and a balanced Mediterranean diet, with 86% of patients subsequently expressing a preference for the latter, it was limited to being a small non-randomized trial of 42 patients, and the Mediterranean diet did not resemble TDA.<sup>24</sup>

Third, objective evidence to support dietary adherence can be inferred from the reductions seen in specific FODMAPs. For example, there was a marked reduction in all FODMAPs within the LFD group (27.7 g/day to 7.6 g/day, with  $< 12$  g per day being the desired cutoff),<sup>25</sup> appropriate reductions with the GFD (ie, fructo- and galacto- oligosaccharides), and for TDA a decrease in fructo-oligosaccharides, lactose, and mannitol (which is to be expected when reducing some gas-producing foods, eg, bread, fruits, dairy, and sweeteners).

Fourth, because of COVID-19, dietary education moved away from face-to-face to virtual consults and was also provided in group settings. We found similar clinical efficacy to dietary therapy irrespective of the mode of educational delivery, with response rates in the group setting being comparable with studies where patients have been seen individually.<sup>16,17</sup> Moving forward, this delivery of care model will have cost-saving implications for healthcare services and alleviate concerns patients may have attending health centers in the current climate.

Current national guidelines demonstrate some differences regarding dietary therapies in IBS.<sup>7–9</sup> Whereas British guidelines recommend TDA as the first choice followed by a LFD, the North American guidelines only mention a LFD.<sup>7–9</sup> Because of insufficient evidence, neither recommends a GFD, although our study (among other recent publications) suggests it deserves future reevaluation.<sup>4</sup> On balancing the efficacy and acceptability of dietary therapies plus the demands they place on healthcare services, we suggest TDA be considered first. Although the LFD and GFD are beneficial, they are costlier, harder to follow, and more inconvenient. Furthermore, their implementation requires specialized and extensive dietetic input, which incurs a substantial burden on healthcare services. Indeed, even within countries with highly established healthcare systems (eg, United Kingdom and United States), there is inequity of GI dietetic services available across regions<sup>26</sup> and a failure to correctly implement a LFD despite it frequently being recommended and prescribed.<sup>27</sup> Because IBS is a global condition, then arguably countries with less

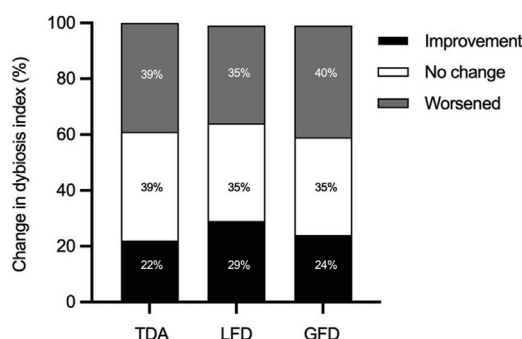


Figure 2. Change in stool dysbiosis index.

established healthcare systems may be falling even shorter of optimally delivering a LFD. Hence, we suggest a GFD or LFD be reserved according to specific patient preferences and with specialist dietetic input. It would also be of interest to evaluate their efficacy in patients not responding to TDA. However, because costs are critical determinants of IBS treatment value to patients and providers, alternate cheaper options should also be considered (eg, antispasmodics, neuromodulators).<sup>28</sup>

The diets reduced total FODMAP intake, mostly in the LFD group compared with TDA and GFD. This suggests a degree of overlap and that moderate FODMAP restriction, as seen with TDA and a GFD, may be similarly effective as a strict LFD. To reintroduce FODMAPs to tolerance and avoid over-restriction, it is important to emphasize that the LFD is altogether a 3-stage process, and that after its strict 4- to 6-week elimination phase comes reintroduction and personalization, all done under dietetic supervision.<sup>6,7</sup> However, real-world Canadian healthcare experience suggests that only 40% satisfactorily complete all 3 phases of the LFD program, implying that a proportion might remain within the strict elimination phase and are at risk of developing overly restrictive eating patterns and nutritional inadequacies.<sup>25</sup> There are suggestions that a “bottom-up” or “FODMAP-gentle” approach to the LFD may overcome its extensive 3-phase program.<sup>4</sup> For example, in the long-term, many patients on a personalized LFD reduce fructan intake to manage their symptoms and facilitate this through purchasing gluten-free or wheat-free products.<sup>29</sup> This raises the hypothesis that a GFD might be an option before considering the complete LFD program. Other reasons for a GFD in IBS are in anti-gliadin antibody positive patients, as well as those with non-celiac gluten/wheat sensitivity.<sup>10,30</sup> Our study, among another recent publications, suggests that a GFD in IBS does not need to be strict as that seen in celiac disease.<sup>30</sup> However, because the GFD generally comes in one form, future studies should determine the level of gluten restriction required to derive symptom benefit, regardless of whether they start with this diet or reach it via a personalized LFD.

The study limitations are similar to previous randomized trials in that dietary intervention was of 4-week duration, and long-term outcomes are relatively unknown.<sup>12</sup> A few studies have demonstrated ongoing efficacy with a GFD and personalized LFD,<sup>23,29</sup> although as mentioned there is currently no guidance regarding gluten reintroduction. The study was also powered to detect a large 35% difference in clinical benefit between the LFD and GFD compared with TDA; thus it was underpowered to detect smaller yet significant differences, potentially leading to a type II error. Interestingly, when combining our results with that of a similarly designed and powered Swedish study,<sup>16</sup> essentially doubling the sample size to ~70 patients per arm, the proportion of responders with a  $\geq 50$ -point reduction in IBS-SSS is

~44% (range 42%–46%) with TDA and ~53% with LFD (range 50%–55%), suggesting a difference of 9%. In our study, a GFD showed 16% gain over TDA. To ascertain whether a 9% to 16% therapeutic gain with a LFD and GFD is significant over TDA, then on the basis of our primary end point, studies with a sample size of more than 950 and almost 300 patients, respectively, would be needed. However, whether this would lead to TDA being displaced from pole position is debatable because of its relative simplicity and minimal healthcare service requirements, and that the LFD and GFD are still viable options that can be considered afterwards. In addition, although our study was geared toward comparing different diets head-to-head, their true benefit (if any) over placebo is unknown in the absence of a control group. Pharmacologic trials in IBS suggest a pooled placebo response rate of approximately 30%,<sup>31</sup> but this is yet to be adequately explored with dietary interventions. We also excluded patients with IBS-constipation on the presumption that reducing FODMAP intake might aggravate constipation and worsen overall symptoms; however, there are emerging data to suggest a LFD might benefit this patient group and, alongside the other dietary interventions, merits further independent study.<sup>16</sup> Other limitations relating to the tools used to assess nutritional intake and nutritional considerations when prescribing dietary therapies are detailed in [Supplementary Discussion](#). Here we also discuss issues regarding the stool normobiotic reference range, and that only 50% of stool samples were collected, which precludes firm conclusions on the stool DI being made.

In conclusion, TDA, GFD, and a LFD are effective approaches in non-constipated IBS. We recommend TDA as the first-choice dietary option because of its widespread availability and patient friendliness. The LFD or GFD are alternative options based on specific patient preferences and with specialist dietetic counseling.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org), and at <https://doi.org/10.1016/j.cgh.2022.02.045>.

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#### Reprint requests

Address requests for reprints to: Dr Imran Aziz, Academic Department of Gastroenterology, Sheffield Teaching Hospitals & Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom. e-mail: [imran.aziz1@nhs.net](mailto:imran.aziz1@nhs.net).

#### CRedit Authorship Contributions

Anupam Rej, MBChB, MRCP (Conceptualization: Supporting; Data curation: Lead; Formal analysis: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)

David S. Sanders, MBChB, MD, FRCP (Conceptualization: Lead; Data curation: Supporting; Formal analysis: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting)

Christian C. Shaw, RD (Data curation: Supporting; Formal analysis: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting)

Rachel Buckle, RD (Data curation: Supporting; Formal analysis: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting)

Nick Trott, RD (Data curation: Supporting; Formal analysis: Supporting; Writing – original draft: Supporting; Writing – review & editing: Supporting)

Anurag Agrawal, MBChB, MRCP (Data curation: Supporting; Writing – review & editing: Supporting)

Imran Aziz, MRCP (Conceptualization: Lead; Data curation: Supporting; Formal analysis: Supporting; Supervision: Lead; Writing – original draft: Lead; Writing – review & editing: Lead)

#### **Conflicts of interest**

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## Supplementary Methods

### *Inclusion and Exclusion Criteria*

Patients with IBS were recruited across 2 secondary care centers in the region of South Yorkshire, United Kingdom (Sheffield Teaching Hospitals and Doncaster Royal Infirmary). The inclusion criteria were adults aged 18 years and older, meeting the Rome IV criteria for IBS-D or IBS-M, and with an IBS-SSS >75. Additional inclusion criteria included being English literate, able to travel to hospital, and having telephone or internet access.

Exclusion criteria were those not meeting the inclusion criteria listed above or anyone with a history of inflammatory bowel disease, celiac disease (as per positive tissue transglutaminase), GI cancer, previous abdominal surgery, scleroderma, poorly controlled diabetes, severe liver/respiratory/cardiac/psychiatric disease (with “severe” defined as repeated flares, recurrent hospital or general practitioner attendances, numerous medications, clinically appearing unwell because of that disease process), memory impairment, pregnant, current dietary interventions, recurrent or current use of probiotics/antibiotics/narcotics, or currently titrated antidepressants (ie, not on a stable dose).

### *Questionnaires*

The following questionnaires were completed before and after dietary intervention:

- (1) IBS-SSS<sup>1</sup>: this is a frequently used assessment in clinical studies where responders rate, over the preceding 10 days, abdominal pain severity, pain frequency, bloating, bowel habit dissatisfaction, and life interferences related to bowel symptoms. The maximum cumulative score available is 500, and subjects can be classified as having no symptoms (<75) to mild (75–175), moderate (175–300), and severe IBS (>300). A reduction of 50 points is considered to confer a clinical improvement and was the primary end point of this study.
- (2) Hospital Anxiety and Depression Scale (HADS)<sup>2</sup>: a psychological screening tool that has in total 14 items, 7 each for depression and anxiety. Each item is rated from 0 (not present) to 3 (maximum), giving a cumulative score for each subscale to range from 0 to 21.<sup>2</sup> A subscale score  $\geq 11$  is used to indicate a clinically significant level of anxiety or depression.
- (3) The patient health questionnaire (PHQ)-12 non-GI somatic symptoms scale<sup>3</sup>: The PHQ-12 records bothersome non-GI symptoms over the past month. The 12 symptoms assessed are back pain, limb pain, headaches, chest pain, dizziness, fainting spells, palpitations, breathlessness, menstrual cramps, dyspareunia, insomnia, and lethargy. Subjects were asked to rate how much they had been troubled by these 12 symptoms over the last 4 weeks as 0 (“not bothered at all”), 1 (“bothered a little”), or 2 (“bothered a lot”). Responses were used to calculate the number of sites reporting somatic symptoms (ranging from 0 to 12) and the somatization severity score (ranging from 0 to 24), which was categorized as minimal ( $\leq 3$ ), low (4–7), medium (8–12), and high ( $\geq 13$ ).
- (4) The IBS quality of life (IBS-QOL) questionnaire<sup>4</sup>: this consists of 34 questions that are summed and averaged for a total score, in addition to 8 subscale scores (Dysphoria, Interference with Activity, Body Image, Health Worries, Food Avoidance, Social Reaction, Sexuality, Social Relationship). Total and subscale scores are transformed to a 0–100 scale. Higher scores indicate better IBS-specific QOL.
- (5) The acceptability of dietary restriction questionnaire is based on the adapted nutrition-related QOL questionnaire.<sup>5</sup> Responses are recorded using a Likert scale, with the responses of agree, neutral, and disagree.
- (6) The food-related QOL questionnaire is a 7-item questionnaire based on the food-related QOL tool (Satisfaction with Food-related Life).<sup>6</sup> Responses are recorded on Likert scale as agree, neutral, or disagree.
- (7) Comprehensive Nutrition Assessment Questionnaire (CNAQ): this is a semiquantitative food frequency questionnaire, consisting of 297 questions, assessing macronutrient and micronutrient intake, as well as FODMAPs, fiber, starch, glycemic index, and glycemic load.<sup>7</sup> The questionnaire asks about food intake over the last 6 months, although the answers range from over the last month to daily. Importantly, we asked individuals not to provide their food intake over the last 6 months (as written on the CNAQ) but rather pre-specified that it has to be over the last 4 weeks only.

### *Stool Samples*

Stool samples were collected both before and after dietary intervention. Sample storage experiments performed by GA-map have shown that fecal samples are stable for GA analysis up to 5 days at room temperature (data not shown), allowing enough time for sending of samples through the post. In our study, the samples were collected from the patient’s address within a day and then batch stored in a  $-80^{\circ}$  freezer until completion of the study. On study completion, samples were shipped on dry ice to Norway for analysis. The GA-map Dysbiosis test was used to analyze samples, which is a gut microbiota DNA analysis tool that can identify and characterize

dysbiosis from a fecal sample.<sup>8</sup> The test allows for mapping of select bacteria and is based on DNA profiling using probes to target variable regions (V3 to V7 regions) of bacteria 16S ribosomal RNA (rRNA) gene to characterize whether bacteria are present.<sup>8</sup> Each probe was designed to target a bacterial species or group on the basis of their 16S rRNA sequence.<sup>8</sup> Probes were selected on ability to differentiate between healthy individuals, IBS, and inflammatory bowel disease.<sup>8</sup> The probe set consisted of 48 probes detecting bacteria within the 6 phyla: Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, Tenericutes, and Verrucomicrobia. On analysis, bacterial profiles were assigned an overall DI index on a scale set from 0 to 5.<sup>8</sup> A DI score of 2 or lower was classified as being within the non-dysbiotic region compared with the normobiotic reference cohort. A DI of greater than 2 was considered to be dysbiotic, with a higher DI number indicating greater dysbiosis from the reference range.<sup>8</sup> Relative bacterial abundance was also supplied for each probe in comparison with the normobiotic reference range, with values ranging from -3 to +3 (dependent upon probe), with -3 being strongly reduced levels of bacteria compared with the reference range and +3 being strongly elevated levels of bacteria. In addition, functional bacterial profiles were given, with functional properties deduced from specific bacteria profiles; the bacterial markers of *Anaerobutyricumhallii*, [*Eubacterium*] *rectale*, and *Faecalibacterium prausnitzii* were used to assess butyrate producing bacteria, *Faecalibacterium prausnitzii* and *Akkermansiamuciniphila* were used to assess gut mucosa protective bacteria, *Faecalibacterium prausnitzii* was used to assess gut intestinal health, *Faecalibacterium prausnitzii*, *Ruminococcusgnavus*, *Proteobacteria*, *Shigella spp.*, and *Escherichia spp.* were used to assess intestinal epithelial barrier, and *Proteobacteria*, *Shigella spp.*, and *Escherichia spp.* were used to assess proinflammatory bacteria.

### Statistical Analysis

Analysis was performed per protocol. All data were analyzed using SPSS version 26 (International Business Machines, Armonk, NY) and GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA). Statistical significance was considered when  $P < .05$ .

Categorical variables were summarized by descriptive statistics, including total numbers and percentages, with comparisons between groups performed using  $\chi^2$

testing, with post hoc tests (if required). Normality was assessed by using the Shapiro-Wilk test. Parametric data were summarized by mean and standard deviation, with the difference across multiple groups performed using one-way analysis of variance, with post hoc tests (if required) using the Bonferroni correction. Within-group comparisons for parametric data were analyzed by using paired  $t$  tests. Non-parametric data were summarized by median and range, with the difference across multiple groups performed using the Kruskal-Wallis test, with post hoc tests performed if required. Within-group comparisons for non-parametric data were performed by using the Wilcoxon test. Missing data were replaced by using the last observation carried forward method. Where no baseline outcome data were available, data were excluded from analysis.

Binary logistic regression was used to assess predictors for response to dietary therapies, with univariate analysis used initially and with multivariate analysis if significance was noted.

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## Supplementary Discussion

### *Nutritional Implications and Limitations*

Nutritional inadequacy can arise after dietary therapies in IBS.<sup>1</sup> In fact, before seeking professional dietary advice, patients with IBS might have restricted eating patterns and fail to meet DRVs for multiple nutrients.<sup>2</sup> In our study, most individuals failed to meet DRVs for total energy intake before intervention. After dietary interventions, reductions in absolute macronutrient and micronutrient counts were observed, with a significant proportion subsequently failing to meet DRVs for certain micronutrients (potassium and iron on TDA, thiamine and magnesium on both LFD and GFD) but not macronutrients. Another noteworthy observation is that more patients were willing to continue with the diet they were allocated than had a symptomatic response. Reasons for this are unclear, but it might be that patients are in pursuit of obsessive healthy eating, which puts them at risk of developing avoidant restrictive food intake disorders and needs to be carefully monitored.<sup>1</sup> In all, this emphasizes the importance of carefully screening patients at high risk of eating disorders before recommending dietary interventions. This can be achieved through the use of simple eating disorder questionnaires (eg, SCOFF) and identifying those with high levels of psychological distress.<sup>3–5</sup>

A limitation of our nutritional analysis was that the food frequency questionnaire tool used (CNAQ) was based on the Australian diet. Although this tool is the most objective tool currently available in the literature and has been used in previous United Kingdom studies,<sup>6</sup> the nutritional and FODMAP assessments may have been underestimated or overestimated. However, in this study, the CNAQ tool was used both before and after intervention to assess change between all 3 groups to ensure consistency.

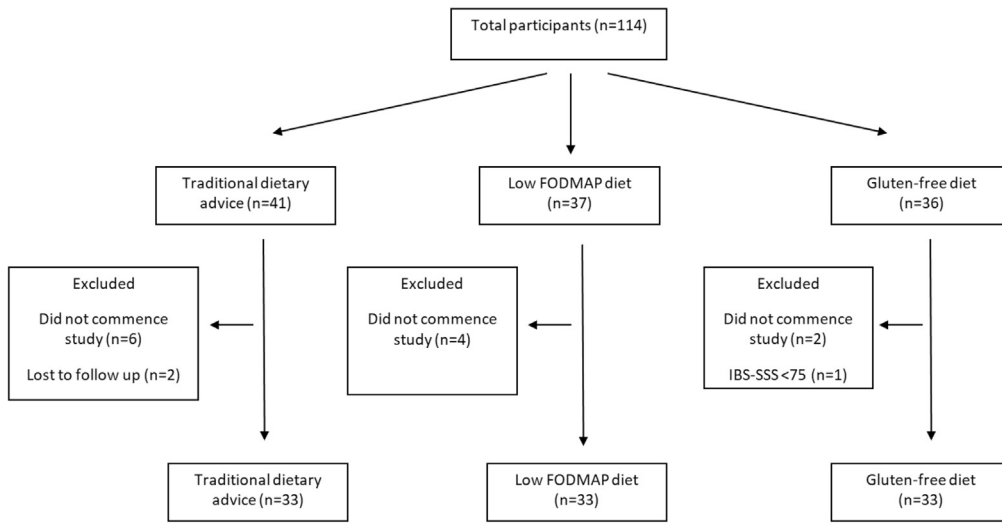
### *Stool Microbial Implications and Limitations*

Diet is thought to be a key environmental component in the composition of the gut microbiome,<sup>7</sup> with the LFD having previously been shown in short-term studies to reduce the proportion of luminal *Bifidobacterium*, as well as total bacterial abundance.<sup>8–10</sup> On the GFD, reduction in *Bifidobacterium* has also been noted, as well as *Faecalibacterium prausnitzii* proportions.<sup>11</sup> Although changes in bacterial abundance after all 3 interventions were noted, the clinical significance of this is unclear, with no significant difference in functional bacterial profiles noted. A previous study using the same method

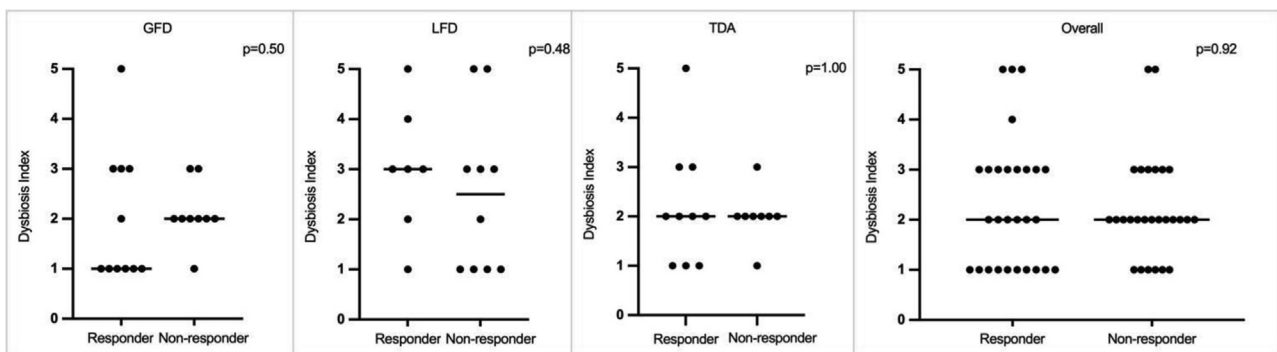
of stool analysis demonstrated that response to a LFD, but not TDA, could be determined from baseline fecal bacterial profiles.<sup>9</sup> However, we were unable to replicate these findings, highlighting the uncertainty in this area, although admittedly our stool sample size was only 50% and underpowered because of the impact of COVID-19. Finally, the stool DI was based on a normobiotic reference range derived from a predominantly Scandinavian cohort,<sup>12</sup> although the purpose of our study was to compare within- and across-group changes after dietary intervention.

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**Supplementary Figure 1.** Consort diagram of patient flow throughout study.



**Supplementary Figure 2.** Baseline stool DI between responders and non-responders to dietary therapy.

**Supplementary Table 1.** Randomized Trials of TDA (vs a low FODMAP Diet) Assessing Whether Patients Allocated TDA Were Advised to Reduce Commonly Consumed Gas-Producing Foods as per Recommendations

Author	Country	Advised to reduce common gas-producing foods as per TDA recommendations?	Detectable reduction in consumption of gas-producing foods with TDA?
Bohn et al <sup>1</sup>	Sweden	Yes	Yes
Eswaran et al <sup>2</sup>	United States	No, instead termed as “modified” diet	No
Zahedi et al <sup>3</sup>	Iran	Partial, only advised avoidance of chewing gums and sweeteners containing polyols	No
Goyal et al <sup>4</sup>	India	No	No
Zhang et al <sup>5</sup>	China	No	No

<sup>1</sup>Böhn L, Störstrud S, Liljebo T, et al. Diet low in FODMAPs reduces symptoms of irritable bowel syndrome as well as traditional dietary advice: a randomized controlled trial. *Gastroenterology* 2015;149:1399–1407.e1392.

<sup>2</sup>Eswaran SL, Chey WD, Han-Markey T, et al. A randomized controlled trial comparing the low FODMAP diet vs modified NICE guidelines in US adults with IBS-D. *Am J Gastroenterol* 2016;111:1824–1832.

<sup>3</sup>Zahedi MJ, Behrouz V, Azimi M. Low fermentable oligo-di-mono-saccharides and polyols diet versus general dietary advice in patients with diarrhea-predominant irritable bowel syndrome: a randomized controlled trial. *J Gastroenterol Hepatol* 2018;33:1192–1199.

<sup>4</sup>Goyal O, Batta S, Nohria S, et al. Low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol diet in patients with diarrhea-predominant irritable bowel syndrome: a prospective, randomized trial. *J Gastroenterol Hepatol* 2021;36:2107–2115.

<sup>5</sup>Zhang Y, Feng L, Wang X, et al. Low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet compared with traditional dietary advice for diarrhea-predominant irritable bowel syndrome: a parallel-group, randomized controlled trial with analysis of clinical and microbiological factors associated with patient outcomes. *Am J Clin Nutr* 2021;113:1531–1545.

**Supplementary Table 2.** Baseline Demographics

Demographics	TDA (n = 33)	LFD (n = 33)	GFD (n = 33)	Overall (n = 99)	Comparison across groups, <i>P</i> value
Female, n (%)	24 (73)	25 (76)	21 (64)	79 (70)	.57
Mean age (SD), y	40 (15)	35 (12)	36 (13)	37 (13)	.22
Mean BMI (SD), kg/m <sup>2</sup>	27 (10)	26 (11)	24 (8)	25 (10)	.33
Mean IBS-SSS (SD)	291 (89)	296 (87)	316 (92)	301 (89)	.47
Mean HADS (SD)	16 (7)	18 (9)	16.5 (9)	17 (8)	.58
Mean PHQ-12 (SD)	9.6 (5)	8.5 (4)	8.4 (4)	8.8 (4)	.41
Mean IBS-QOL (SD)	52 (18)	51 (21)	60 (26)	54 (22)	.15
Index of Multiple Deprivation quintiles					
Q1, n (%) – most deprived	7 (21)	9 (27)	12 (36)	28 (29)	.1
Q2, n (%)	3 (9)	9 (27)	1 (3)	13 (13)	
Q3, n (%)	10 (30)	6 (18)	8 (24)	24 (25)	
Q4, n (%)	7 (21)	7 (21)	4 (12)	18 (18)	
Q5, n (%) – least deprived	6 (18)	2 (6)	7 (21)	15 (15)	

BMI, body mass index; HADS, Hospital Anxiety and Depression scale; PHQ-12, Patient Health Questionnaire-12; SD, standard deviation.



**Supplementary Table 3.** HADS, PHQ-12, and IBS-QOL

Symptom score	Intervention						Comparison of change across groups, <i>P</i> value
	TDA		LFD		GFD		
	Baseline	Week 4	Baseline	Week 4	Baseline	Week 4	
HADS anxiety, mean (SD)	9.5 (4.4)	9.5 (4.4)	10.6 (5.4)	8.9 (5.1)	9.8 (5.4)	8.4 (4.9)	.08
HADS depression, mean (SD)	6.8 (3.3)	7.6 (3.5)	7.6 (4.5)	6.5 (5.2)	6.7 (4.6)	6.4 (5.0)	.03
PHQ-12 score, mean (SD)	9.6 (4.7)	8.7 (3.7)	8.5 (4.0)	7.7 (3.7)	8.4 (3.6)	7.9 (4.2)	.8
<b>IBS-QOL</b>							
IBS-QOL score, mean (SD)	52 (18)	55 (21)	51 (21)	61 (24)	60 (26)	65 (26)	.10
Dysphoria	51 (22)	55 (24)	48 (26)	65 (27)	60 (32)	65 (32)	<.01
Interference with activity	49 (20)	54 (25)	45 (27)	56 (27)	57 (29)	62 (28)	.21
Body image	52 (23)	55 (21)	45 (25)	54 (25)	63 (25)	67 (30)	.43
Health worries	56 (20)	54 (25)	62 (25)	69 (25)	62 (27)	69 (24)	.09
Food avoidance	39 (26)	38 (29)	45 (32)	48 (27)	45 (33)	47 (30)	.88
Social reaction	51 (22)	57 (26)	51 (28)	62 (29)	62 (26)	66 (28)	.37
Sexuality	62 (30)	65 (30)	70 (30)	70 (28)	75 (27)	75 (31)	.83
Social relationship	62 (25)	67 (24)	64 (29)	68 (29)	70 (25)	75 (26)	1.00

HADS, Hospital Anxiety and Depression scale; PHQ-12, Patient Health Questionnaire-12; SD, standard deviation.

**Supplementary Table 4.** Proportion of Individuals Meeting DRVs

Nutritional parameter	Intervention								
	TDA			LFD			GFD		
	Baseline DRV met (%)	Week 4 DRV met (%)	Baseline vs Week 4, <i>P</i> value	Baseline DRV met (%)	Week 4 DRV met (%)	Baseline vs Week 4, <i>P</i> value	Baseline DRV met (%)	Week 4 DRV met (%)	Baseline vs Week 4, <i>P</i> value
Energy, <i>kcal/d</i>	41	29	.31	45	26	.11	55	42	.32
Protein, <i>g/d</i>	91	74	.06	81	72	.38	88	82	.49
Carbohydrate, <i>g/d</i>	44	41	.81	53	38	.21	42	42	1.00
Fat, <i>g/d</i>	74	76	.78	53	50	.80	61	61	1.00
Dietary fiber, <i>g/d</i>	62	38	.05	38	28	.42	55	39	.22
Folate, $\mu\text{g/d}$	97	85	.09	88	72	.12	100	94	.55
Thiamine, <i>mg/d</i>	94	88	.39	94	63	<.01	97	79	.02
Riboflavin, <i>mg/d</i>	85	88	.72	84	78	.52	91	91	1.00
Niacin, <i>mg/d</i>	88	85	.72	81	58	.05	91	85	.45
Vitamin C, <i>mg/d</i>	100	100	1.00	97	91	.30	100	100	1.00
Sodium, <i>mg/d</i>	79	71	.40	78	69	.40	67	52	.21
Potassium, <i>mg/d</i>	79	53	.02	56	34	.08	67	52	.21
Magnesium, <i>mg/d</i>	79	62	.11	63	38	<.05	79	55	.04
Calcium, <i>mg/d</i>	82	68	.16	75	59	.18	85	70	.14
Phosphorus, <i>mg/d</i>	100	97	.31	100	97	.31	100	100	1.00
Iron, <i>mg/d</i>	71	47	<.05	61	52	.44	61	52	.46
Zinc, <i>mg/d</i>	79	79	1.00	81	69	.37	91	79	.17

**Supplementary Table 5.** Change in DI by Intervention and Responders

	Change in DI			Comparison of responders vs non-responders, <i>P</i> value
	Improved, n (%)	No change, n (%)	Worsened, n (%)	
<b>TDA</b>				
Responders	3 (30)	2 (20)	5 (50)	.18
Non-responders	1 (13)	5 (63)	2 (25)	
<b>LFD</b>				
Responders	2 (29)	2 (29)	3 (43)	.84
Non-responders	3 (30)	4 (40)	3 (30)	
<b>GFD</b>				
Responders	2 (18)	4 (36)	5 (46)	.72
Non-responders	3 (33)	3 (33)	3 (33)	
<b>Overall</b>				
Responders	7 (25)	8 (29)	13 (46)	.37
Non-responders	7 (26)	12 (44)	8 (30)	

**Supplementary Table 6.** Functional Bacterial Profiles With Dietary Interventions

	TDA			LFD			GFD		
	Baseline, n (%)	Follow-up, n (%)	<i>P</i> value	Baseline, n (%)	Follow-up, n (%)	<i>P</i> value	Baseline, n (%)	Follow-up, n (%)	<i>P</i> value
Low levels of butyrate producing bacteria	5 (28)	2 (22)	.70	4 (24)	2 (12)	.37	3 (15)	5 (25)	.43
Low levels of gut mucosa protective bacteria	3 (17)	3 (17)	1.00	3 (18)	4 (24)	.67	4 (20)	6 (30)	.47
Low levels of <i>F. prausnitzii</i>	0 (0)	3 (17)	.07	3 (18)	2 (12)	.63	2 (10)	4 (20)	.38
Imbalance between selected gut barrier protective and potentially harmful bacteria	2 (11)	2 (11)	1.00	4 (24)	5 (29)	.70	6 (30)	3 (15)	.26
High levels of proinflammatory bacteria	1 (6)	1 (6)	1.00	4 (24)	4 (18)	.67	0 (0)	1 (5)	.31

**Supplementary Table 7.** Bacterial Abundance Following TDA

Genus/species	Class	Phylum	DI at follow-up vs baseline	<i>P</i> value
Actinobacteria	Actinobacteria	Actinobacteria	No difference	.67
Actinomycetales	Actinobacteria	Actinobacteria	No difference	.18
Bifidobacterium spp.	Actinobacteria	Actinobacteria	No difference	1.00
Alistipes	Alistipes	Bacteroidetes	No difference	.32
Alistipes onderdonkii	Alistipes	Bacteroidetes	No difference	.66
Bacteroides fragilis	Bacteroides	Bacteroidetes	No difference	.56
Bacteroides spectinophilus	Bacteroides	Bacteroidetes	No difference	.08
Bacteroides spp.	Bacteroides	Bacteroidetes	No difference	.26
Bacteroides spp., Prevotella spp.	Bacteroides	Bacteroidetes	No difference	.33
Bacteroides stercoris	Bacteroides	Bacteroidetes	No difference	.71
Bacteroides zooglyphiformans	Bacteroides	Bacteroidetes	No difference	.26
Parabacteroides johnsonii	Parabacterioides	Bacteroidetes	No difference	1.00
Parabacteroides spp.	Parabacterioides	Bacteroidetes	No difference	.32
Firmicutes	Negativicutes/Clostridia	Firmicutes	No difference	.19
Bacilli	Bacilli	Firmicutes	No difference	.60
Catenibacterium	Erysipelotrichia	Firmicutes	No difference	1.00
Clostridia	Clostridia	Firmicutes	No difference	.72
Clostridium methylpentosum	Ruminiclostridium	Firmicutes	No difference	1.00
Clostridium sp.	Clostridia	Firmicutes	No difference	1.00
Coprobacillus cateniformis	Erysipelotrichia	Firmicutes	No difference	1.00
Dialister invisus	Negativicutes	Firmicutes	No difference	1.00
Dialister invisus, Megasphaera micronuciformis	Negativicutes	Firmicutes	No difference	.32
Dorea spp.	Clostridia	Firmicutes	Decreased	<.05
Eubacterium bifforme	Clostridia	Firmicutes	No difference	.26
Eubacterium hallii	Clostridia	Firmicutes	No difference	.56
Eubacterium rectale	Clostridia	Firmicutes	No difference	1.00
Eubacterium siraeum	Clostridia	Firmicutes	No difference	.41
Faecalibacterium prausnitzii	Clostridia	Firmicutes	No difference	.53
Lachnospiraceae	Clostridia	Firmicutes	No difference	.71
Lactobacillus ruminis, Pediococcus acidilactici	Bacilli	Firmicutes	No difference	.16
Lactobacillus spp.	Bacilli	Firmicutes	No difference	.76
Lactobacillus spp. 2	Bacilli	Firmicutes	No difference	.71
Phascolarctobacterium sp.	Negativicutes	Firmicutes	No difference	.32
Ruminococcus albus, R bromii	Clostridia	Firmicutes	No difference	.78
Ruminococcus gnavus	Clostridia	Firmicutes	No difference	.56
Streptococcus agalactiae, Eubacterium rectale	Bacilli	Firmicutes	No difference	.56
Streptococcus salivarius ssp. Thermophiles, S sanguinis	Bacilli	Firmicutes	No difference	.71



Supplementary Table 7. Continued

Genus/species	Class	Phylum	DI at follow-up vs baseline	<i>P</i> value
<i>Streptococcus salivarius</i> ssp. <i>Thermophilus</i>	Bacilli	Firmicutes	No difference	1.00
<i>Streptococcus</i> spp.	Bacilli	Firmicutes	No difference	.78
<i>Streptococcus</i> spp. 2	Bacilli	Firmicutes	No difference	.85
<i>Veillonella</i> spp.	Negativicutes	Firmicutes	No difference	.60
Firmicutes (various)	—	Firmicutes/Tenericutes/ Bacteroidetes species	No difference	1.00
Proteobacteria	—	Proteobacteria	No difference	.41
<i>Acinetobacter junii</i>	Gammaproteobacteria	Proteobacteria	No difference	1.00
Enterobacteriaceae	Gammaproteobacteria	Proteobacteria	No difference	.16
<i>Shigella</i> spp., <i>Escherichia</i> spp	Gammaproteobacteria	Proteobacteria	No difference	1.00
<i>Mycoplasma hominis</i>	Mollicutes	Tenericutes	No difference	1.00
<i>Akkermansia muciniphila</i>	Verrucomicrobiae	Verrucomicrobia	No difference	.41

**Supplementary Table 8.** Bacterial Abundance Following a Low FODMAP Diet

Genus/species	Class	Phylum	Abundance at follow-up vs baseline	P value
Actinobacteria	Actinobacteria	Actinobacteria	Decreased	<.05
Actinomycetales	Actinobacteria	Actinobacteria	No difference	.56
Bifidobacterium spp.	Actinobacteria	Actinobacteria	No difference	.16
Alistipes	Alistipes	Bacteroidetes	Increased	.02
Alistipes onderdonkii	Alistipes	Bacteroidetes	No difference	.18
Bacteroides fragilis	Bacteroides	Bacteroidetes	Decreased	.02
Bacteroides pectinophilus	Bacteroides	Bacteroidetes	No difference	.71
Bacteroides spp.	Bacteroides	Bacteroidetes	No difference	.38
Bacteroides spp., Prevotella spp.	Bacteroides	Bacteroidetes	No difference	.18
Bacteroides stercoris	Bacteroides	Bacteroidetes	No difference	1.00
Bacteroides zooglyphiformans	Bacteroides	Bacteroidetes	No difference	.53
Parabacteroides johnsonii	Parabacterioides	Bacteroidetes	Increased	<.05
Parabacteroides spp.	Parabacterioides	Bacteroidetes	No difference	.13
Firmicutes	Negativicutes/Clostridia	Firmicutes	No difference	.18
Bacilli	Bacilli	Firmicutes	No difference	.16
Catenibacterium	Erysipelotrichia	Firmicutes	No difference	.32
Clostridia	Clostridia	Firmicutes	No difference	.38
Clostridium methylpentosum	Ruminiclostridium	Firmicutes	Increased	.03
Clostridium sp.	Clostridia	Firmicutes	No difference	.32
Coprobacillus cateniformis	Erysipelotrichia	Firmicutes	No difference	.32
Dialister invisus	Negativicutes	Firmicutes	No difference	.32
Dialister invisus, Megasphaera micronuciformis	Negativicutes	Firmicutes	No difference	.66
Dorea spp.	Clostridia	Firmicutes	No difference	.48
Eubacterium bifforme	Clostridia	Firmicutes	No difference	.16
Eubacterium hallii	Clostridia	Firmicutes	No difference	.48
Eubacterium rectale	Clostridia	Firmicutes	No difference	.76
Eubacterium siraeum	Clostridia	Firmicutes	No difference	1.00
Faecalibacterium prausnitzii	Clostridia	Firmicutes	No difference	.74
Lachnospiraceae	Clostridia	Firmicutes	Increased	.01
Lactobacillus ruminis, Pediococcus acidilactici	Bacilli	Firmicutes	No difference	.32
Lactobacillus spp.	Bacilli	Firmicutes	No difference	.32
Lactobacillus spp. 2	Bacilli	Firmicutes	No difference	.26
Phascolarctobacterium sp.	Negativicutes	Firmicutes	No difference	.16
Ruminococcus albus, R bromii	Clostridia	Firmicutes	No difference	.71
Ruminococcus gnavus	Clostridia	Firmicutes	No difference	.89
Streptococcus agalactiae, Eubacterium rectale	Bacilli	Firmicutes	No difference	.48
Streptococcus salivarius ssp. Thermophiles, S sanguinis	Bacilli	Firmicutes	No difference	.48

Supplementary Table 8. Continued

Genus/species	Class	Phylum	Abundance at follow-up vs baseline	<i>P</i> value
<i>Streptococcus salivarius</i> ssp. <i>Thermophilus</i>	Bacilli	Firmicutes	No difference	.32
<i>Streptococcus</i> spp.	Bacilli	Firmicutes	No difference	.06
<i>Streptococcus</i> spp. 2	Bacilli	Firmicutes	No difference	.19
<i>Veillonella</i> spp.	Negativicutes	Firmicutes	No difference	.21
Firmicutes (various)	—	Firmicutes/Tenericutes/ Bacteroidetes species	No difference	.66
Proteobacteria	—	Proteobacteria	No difference	.23
<i>Acinetobacter junii</i>	Gammaproteobacteria	Proteobacteria	No difference	1.00
Enterobacteriaceae	Gammaproteobacteria	Proteobacteria	No difference	.66
<i>Shigella</i> spp., <i>Escherichia</i> spp	Gammaproteobacteria	Proteobacteria	No difference	.16
<i>Mycoplasma hominis</i>	Mollicutes	Tenericutes	No difference	1.00
<i>Akkermansia muciniphila</i>	Verrucomicrobiae	Verrucomicrobia	No difference	.20

Supplementary Table 9. Bacterial Abundance Following a GFD

Genus/species	Class	Phylum	Abundance at follow-up vs baseline	P value
Actinobacteria	Actinobacteria	Actinobacteria	Reduced	.03
Actinomycetales	Actinobacteria	Actinobacteria	No difference	.41
Bifidobacterium spp.	Actinobacteria	Actinobacteria	No difference	.08
Alistipes	Alistipes	Bacteroidetes	No difference	.37
Alistipes onderdonkii	Alistipes	Bacteroidetes	No difference	1.00
Bacteroides fragilis	Bacteroides	Bacteroidetes	No difference	.32
Bacteroides pectinophilus	Bacteroides	Bacteroidetes	No difference	.48
Bacteroides spp.	Bacteroides	Bacteroidetes	No difference	.74
Bacteroides spp., Prevotella spp.	Bacteroides	Bacteroidetes	No difference	1.00
Bacteroides stercoris	Bacteroides	Bacteroidetes	No difference	.16
Bacteroides zoogloeiformans	Bacteroides	Bacteroidetes	No difference	1.00
Parabacteroides johnsonii	Parabacterioides	Bacteroidetes	Reduced	.01
Parabacteroides spp.	Parabacterioides	Bacteroidetes	No difference	.26
Firmicutes	Negativicutes/Clostridia	Firmicutes	No difference	1.00
Bacilli	Bacilli	Firmicutes	No difference	.21
Catenibacterium mitsuokai	Erysipelotrichia	Firmicutes	No difference	1.00
Clostridia	Clostridia	Firmicutes	No difference	.78
Clostridium methylpentosum	Ruminiclostridium	Firmicutes	No difference	.26
Clostridium sp.	Clostridia	Firmicutes	No difference	1.00
Coprobacillus cateniformis	Erysipelotrichia	Firmicutes	No difference	1.00
Dialister invisus	Negativicutes	Firmicutes	No difference	.32
Dialister invisus, Megasphaera micronuciformis	Negativicutes	Firmicutes	No difference	.05
Dorea spp.	Clostridia	Firmicutes	No difference	1.00
Eubacterium bifforme	Clostridia	Firmicutes	No difference	.08
Eubacterium hallii	Clostridia	Firmicutes	No difference	.27
Eubacterium rectale	Clostridia	Firmicutes	Reduced	.02
Eubacterium siraeum	Clostridia	Firmicutes	No difference	.52
Faecalibacterium prausnitzii	Clostridia	Firmicutes	No difference	.21
Lachnospiraceae	Clostridia	Firmicutes	No difference	.32
Lactobacillus ruminis, Pediococcus acidilactici	Bacilli	Firmicutes	No difference	.56
Lactobacillus spp.	Bacilli	Firmicutes	No difference	.56
Lactobacillus spp. 2	Bacilli	Firmicutes	No difference	.33
Phascolarctobacterium sp.	Negativicutes	Firmicutes	No difference	.08
Ruminococcus albus, R bromii	Clostridia	Firmicutes	Reduced	.04
Ruminococcus gnavus	Clostridia	Firmicutes	No difference	.17
Streptococcus agalactiae, Eubacterium rectale	Bacilli	Firmicutes	No difference	.16
Streptococcus salivarius ssp. Thermophiles, S sanguinis	Bacilli	Firmicutes	No difference	.06

Supplementary Table 9. Continued

Genus/species	Class	Phylum	Abundance at follow-up vs baseline	P value
Streptococcus salivarius ssp. Thermophilus	Bacilli	Firmicutes	No difference	.10
Streptococcus spp.	Bacilli	Firmicutes	No difference	.59
Streptococcus spp. 2	Bacilli	Firmicutes	No difference	.42
Veillonella spp.	Negativicutes	Firmicutes	No difference	.77
Firmicutes (various)	—	Firmicutes/Tenericutes/Bacteroidetes species	No difference	.10
Proteobacteria	—	Proteobacteria	No difference	.41
Acinetobacter junii	Gammaproteobacteria	Proteobacteria	No difference	1.00
Enterobacteriaceae	Gammaproteobacteria	Proteobacteria	No difference	1.00
Shigella spp., Escherichia spp	Gammaproteobacteria	Proteobacteria	No difference	.32
Mycoplasma hominis	Mollicutes	Tenericutes	No difference	1.00
Akkermansia muciniphila	Verrucomicrobiae	Verrucomicrobia	No difference	.10

Supplementary Table 10. Binary Logistic Regression Analysis of Clinical Factors Associated With a Response to Dietary Therapies

Variable	Intervention			
	TDA	LFD	GFD	Overall
	OR (CI)	OR (CI)	OR (CI)	OR (CI)
Age (y)	1.04 (1.00 –1.10)	0.99 (0.94 –1.05)	0.99 (0.94 –1.05)	1.00 (0.98 –1.04)
Gender				
Male	1	1	1	1
Female	0.50 (0.10 –2.44)	1.67 (0.32 –8.59)	0.62 (0.15 –2.58)	0.81 (0.34 –1.93)
IBS subtype				
IBS-D	1	1	1	1
IBS-M	0.40 (0.07 –2.42)	0.32 (0.06 –1.62)	1.69 (0.34 –8.40)	0.65 (0.26 –1.62)
IMD quintiles				
Q1–3	1	1	1	1
Q4–5	1.69 (0.42 –6.72)	4.14 (0.71 –24.16)	0.29 (0.06 –1.32)	1.17 (0.51 –2.69)
Somatization severity				
Minimal	1	1	1	1
Low	1.43 (0.10 –20.44)	1.50 (0.10 –23.07)	4.00 (0.27 –58.56)	1.69 (0.41 –6.98)
Medium	1.67 (0.12 –24.26)	0.11 (0.01 –1.52)	4.50 (0.31 –65.23)	0.90 (0.22 –3.63)
High	2.50 (0.16 –38.60)	0.33 (0.02 –5.33)	0.50 (0.02 –12.90)	0.82 (0.18 –3.74)
HADS anxiety levels (clinical)				
Normal	1	1	1	1
Abnormal	0.46 (0.11 –1.96)	0.53 (0.13 –2.14)	0.40 (0.10 –1.68)	0.51 (0.23 –1.14)
HADS depression levels (clinical)				
Normal	1	1	1	1
Abnormal	1.21 (0.15 –9.76)	0.25 (0.04 –1.54)	0.21 (0.03 –1.32)	0.38 (0.13 –1.12)

HADS, Hospital Depression and Anxiety scale; IMD, Index of Multiple Deprivation.