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Impact of HADS Anxiety and Depression Scores on the Efficacy of Dietary Interventions for Irritable Bowel Syndrome

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ABSTRACT

Background: Anxiety and depression are associated strongly with irritable bowel syndrome (IBS). Dietary therapies are used increasingly in the management of IBS, but the impact of common mental disorders on response to these has not been well studied.

Aims: To examine whether symptoms compatible with common mental disorders influence response to dietary interventions.

Methods: Prospective cohort study of adults, with either diarrhoea-predominant or mixed bowel habits, IBS Severity Scoring System [IBS-SSS] score ≥ 75 points. Participants completed the Hospital Anxiety and Depression score (HADS) and attended initially for British Dietary Association advice for IBS. IBS-SSS was re-checked 3 months later to assess response. If primary endpoint (≥ 50 point decrease in IBS-SSS) was not achieved, patients were offered low fermentable oligo-, di- and monosaccharides and polyol diet and repeated IBS-SSS after another 3 months. Secondary endpoints included of change in IBS-SSS and effect of symptom severity on response.

Results: In total, 448 patients took part, average age of 42 years and 79.0% were female. 69.9% of participants had HADS-A scores ≥ 8 and 39.3% with HADS-D scores ≥ 8. Average IBS-SSS score at baseline was 290 (SD 86). No significant difference was noted in achievement of the primary endpoint according to HADS-A scores (53.4% vs. 62.2% by ITT in those with HADS-A ≥ 8 vs. HADS-A < 8, $p = 0.09$). Patients with HADS-D ≥ 8 were significantly less likely to achieve the primary endpoint compared with those with HADS-D < 8 (43.8% vs. 64.0% by ITT, $p < 0.01$).

Conclusion: Understanding psychological profile of patients can help predicting their response to IBS dietary interventions.

1 | Introduction

Irritable bowel syndrome (IBS) is a common chronic gastrointestinal disorder, characterised by abdominal pain associated with a change in either stool form or frequency. The condition affects 5%–10% of people globally [1]. It is widely accepted to be a disorder of the gut–brain axis and, as such, psychological comorbidity is an important mediator of symptoms, in terms of both reporting and persistence, as well as their response to therapies [2–4]. Common mental disorders, such as anxiety and depression, are associated strongly with IBS [5]. In addition, brain–gut behavioural treatments, such as cognitive behavioural therapy

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and gut-directed hypnotherapy, are efficacious in IBS [6]. Up to 50% of patients with comorbid common mental disorders and IBS develop the gastrointestinal symptoms before the onset of symptoms compatible with a common mental disorder, further underlining the potential association between these conditions [7].

Patients, however, are often more inclined to attribute IBS symptoms to dietary factors, whether through food intolerance or non-specific motility disturbances associated with eating [8]. Much attention has, therefore, been focused on the role of dietary therapies in the management of IBS in recent years. These range from empiric basic dietary approaches, such as those recommended by the British Dietary Association (BDA) and the National Institute for Health and Care Excellence (NICE) [9], which include eating small regular meals, maintaining hydration, reducing fruit intake and avoiding caffeine, alcohol and carbonated beverages, to more complex diets [10]. Fermentable oligo-, di- and monosaccharides and polyols (FODMAPs) are associated with osmotic and fermentation effects, which may contribute to IBS symptoms. Their restriction has been shown to reduce symptoms such as abdominal pain, bloating and distension, as well as improving abnormal bowel habit [11, 12].

Although the low FODMAP diet represents one of the most exciting developments in the field of IBS in recent years, it is not without drawbacks, which include being labour intensive, restrictive, expensive and requiring input from a trained dietitian. Common mental disorders may be associated with the degree of response to treatment in IBS, with one study showing that treatment with either desipramine or cognitive behavioural therapy was less likely to be effective if comorbid depression was present [12]. In a large randomised controlled trial of low-dose amitriptyline as second-line treatment for IBS in primary care, a larger treatment effect was noted in patients with lower baseline anxiety scores [13]. However, the impact of common mental disorders on response to dietary therapies has not been well studied. We, therefore, attempted to ascertain whether symptoms compatible with common mental disorders influence response to dietary interventions in IBS.

2 | Materials and Methods

2.1 | Participants

Patients with a diagnosis of IBS with diarrhoea (IBS-D) or mixed bowel habits (IBS-M) were recruited from community or hospital-based referrals to the general gastroenterology clinics at Tallaght University Hospital. This is an academic medical centre serving a population in southwest Dublin, Ireland, of approximately 400,000. The hospital research ethics committee approved the protocol, and each study participant gave informed consent. Potential participants were screened by a consultant gastroenterologist at a hospital appointment. To be included, patients needed to meet Rome-IV criteria for IBS, with recurrent abdominal pain on average at least 1 day per week during the previous 3 months, which was associated with two or more of the following: related to defaecation, associated with a change in stool form or associated with a change in stool frequency [14]. Stool form was assessed using the Bristol stool form scale [15].

Prior to inclusion, patients were required to have undergone investigation to exclude organic disease that may mimic IBS. Patients ≥ 45 years, or with red flag features, including nocturnal diarrhoea, anaemia, CRP ≥ 5 g/L, faecal calprotectin $\geq 50\,\mu$g/g, weight loss, haematochaezia or a family history of either inflammatory bowel disease or colorectal cancer, required a negative colonoscopy, with biopsies to exclude microscopic colitis, prior to study entry [16, 17]. Patients < 45 years without alarm features and a negative stool calprotectin ($< 50\,\mu$g/g) did not require colonoscopy. All patients were screened serologically for coeliac disease and thyroid function tests were performed. Testing for bile acid diarrhoea is not available in our hospital and was, therefore, not part of the diagnostic work-up.

Patients were excluded if they did not speak English, were unable to understand verbal and written instructions, were pregnant, were < 18 years of age or had a history of intestinal resection. Patients with malnutrition or conditions requiring other dietary treatments, such as coeliac disease or diabetes mellitus, were also excluded. Finally, patients with a history of eating disorders or disordered eating were ineligible due to the concerns about the utilisation of a potentially restrictive diet. This was screened for during the clinical history.

2.2 | Clinical Assessments

Demographic and basic clinical information were obtained via clinical notes review. Patients were asked to report any medicines or probiotics they had taken for IBS. Symptoms were assessed using the IBS severity scoring system (IBS-SSS), which is a validated questionnaire that assesses presence, severity and frequency of abdominal pain, presence and severity of abdominal distension, satisfaction with bowel habit and degree to which IBS symptoms are affecting, or interfering with, the individual's life [15]. The maximum score is 500. Mild, moderate or severe symptoms are indicated by scores of 75–174, 175–299 or 300–500, respectively. Presence of symptoms compatible with a common mental disorder was assessed using the hospital anxiety and depression scale (HADS), a self-rating scale containing two subscales measuring symptoms of anxiety (HADS-A) or depression (HADS-D) during the previous week [18]. A score of ≥ 8 for either HADS-A or HADS-D was considered abnormal, as previously recommended [19].

2.3 | Dietary Intervention

The dietary intervention was delivered in two stages. The first stage was in a group setting and consisted of verbal and written instructions based on BDA/NICE-approved dietary guidance for IBS. Patients were asked to adhere to these instructions and to return for follow-up 3 months later, when the IBS-SSS score was repeated. If there was no improvement in symptoms after the first stage of dietary advice, the patient was invited to attend for one-to-one instruction on the low FODMAP diet, consisting of a 1-h session with an experienced, FODMAP-trained dietitian. The session included education on the basic principles of the low FODMAP diet, with patients instructed to restrict foods containing high or moderate amounts of all types of FODMAPs and to consume only foods that contained no or low amounts of

FODMAPs. The interventions were delivered either in person or via video conference from March 2020 onwards, due to the impact of the Coronavirus pandemic. Group and one-to-one interventions on the video conference platform were delivered via Attend Anywhere, a web-based platform. The verbal instructions and written materials provided to patients throughout the intervention were consistent throughout the study period. All interventions were delivered by two senior dietitians working in a specific purpose functional gastrointestinal disease service with more than 5 years experience in gastroenterology at secondary care level. This continued throughout the intervention in both the in person and video conference format. Participants were instructed to follow the low FODMAP diet strictly, from the beginning of week 1 to the end of week 6, at which point they underwent telephone review. At this point, symptomatic response after FODMAP restriction was assessed using the Global Symptom Question (GSQ) ('Do you currently have satisfactory relief of your gut symptoms?'). If the patient answered 'yes', they were educated on the reintroduction phase and, if not, they were instructed to return to their habitual diet. The reintroduction phase consisted of reintroducing one FODMAP subgroup per week, except for oligosaccharides, while monitoring symptoms. The IBS-SSS was then repeated 3 months after FODMAP restriction began to assess symptomatic response formally.

2.4 | Objectives and Outcomes

The primary objective was to assess the benefit of a two-stage dietary intervention for IBS-D or IBS-M according to the presence or absence of symptoms of anxiety or depression at baseline. The null hypothesis was that the presence of such symptoms would not influence treatment response. The primary endpoint measure was either a symptomatic response, defined by a decrease in IBS-SSS score of ≥ 50 points, or symptomatic remission, defined by achieving an overall-IBS-SSS score < 75 [15], at either of the two stages. The key secondary endpoint was the decrease in IBS-SSS score from baseline. Other secondary objectives included assessing whether response according to severity of symptoms differed based on HADS-A or HADS-D scores and whether a difference was noted based on those scores in the likelihood of response to the two individual stages of the intervention.

2.5 | Statistical Analysis

As this was not a clinical trial, but a description of the effectiveness of an intervention in usual clinical practice, no power calculation was performed. All patients lost to follow-up for the purposes of our calculations were assumed to have failed the intervention. Regarding the primary endpoint significance was estimated using a two-tailed Fisher's exact test. Regarding the secondary endpoint of difference in IBS-SSS from baseline significance was estimated using an independent samples *t*-test.

3 | Results

Between 25 September 2017, and 27 January 2021, 503 patients with IBS were invited to take part and 448 (89.1%) attended for first-line dietary advice and were included in the intention-to-treat analysis. Participant demographics and baseline

TABLE 1 | Baseline characteristics of all included participants.

	All participants ($n = 448$)	HADS-A ≥ 8 ($n = 313$)	HADS-A < 8 ($n = 135$)	*p*-value	HADS-D ≥ 8 ($n = 176$)	HADS-D < 8 ($n = 272$)	*p*-value
Age							
Mean (range)	42 (16–85)	42 (16–85)	44 (17–79)	0.19	44 (16–85)	41 (16–79)	0.03
Sex							
Male	94 (21.0%)	59 (18.8%)	35 (25.9%)	0.10	28 (15.9%)	66 (24.3%)	0.04
Female	354 (79.0%)	254 (81.2%)	100 (74.1%)		148 (84.1%)	206 (75.7%)	
IBS subtype							
IBS-D	371 (82.8%)	251 (80.2%)	120 (88.9%)	0.02	144 (81.8%)	227 (83.5%)	0.70
IBS-M	77 (17.2%)	62 (19.8%)	15 (11.1%)		32 (18.2%)	45 (16.5%)	
IBS severity							
Mild	48 (11%)	24 (7.6%)	24 (17.8%)	< 0.01	8 (4.5%)	40 (14.7%)	< 0.01
Moderate	182 (41%)	125 (39.9%)	57 (42.2%)	0.92	52 (29.5%)	130 (47.8%)	< 0.01
Severe	218 (49%)	164 (52.4%)	54 (40.0%)	0.02	116 (65.9%)	102 (37.5%)	< 0.01
Therapies for IBS							
Antispasmodics	97 (22%)	70 (22.4%)	27 (20.0%)	0.62	45 (25.6%)	52 (19.1%)	0.13
Anti-diarrhoeals	38 (8%)	25 (8.0%)	13 (9.6%)	0.58	15 (8.5%)	23 (8.5%)	1.00
Probiotics	41 (9%)	26 (8.3%)	15 (11.1%)	0.37	11 (6.3%)	30 (11.0%)	0.09

characteristics are shown in Table 1. Of these, 347 (77.5%) returned their follow-up questionnaire and were included in the per-protocol (PP) analysis. The average age of these 448 participants was 42 years (range 16–85 years), and 354 (79.0%) were female. There were 313 (69.9%) participants with HADS-A scores ≥ 8 and 176 (39.3%) with HADS-D scores ≥ 8. The average IBS-SSS score was 290 (SD 86). Severe symptoms on the IBS-SSS were more likely in individuals with either a HADS-A or HADS-D score of ≥ 8 (52.4% in those with a HADS-A score ≥ 8 vs. 40.0% in those with a HADS-A score < 8, $p = 0.02$, 65.9% in those with a HADS-D score ≥ 8 vs. 37.5% in those with a HADS-A score < 8, $p < 0.01$). Overall, 130 patients (29.0%) were using antispasmodics, anti-diarrhoeals or probiotics for their IBS with similar frequency in those with normal or abnormal HADS scores.

In total, 202 (45.1% by ITT and 58.2% by PP analysis) achieved the primary endpoint after BDA/NICE-approved dietary guidance (Figure 1). The 145 patients who failed to achieve the endpoint after BDA/NICE-approved dietary guidance were then offered the option of commencing a low FODMAP diet or discontinuing dietary management. Of these, 94 (64.8%) patients attended for instruction on the low FODMAP diet and 84 (89.4%) of 94 patients returned their follow-up questionnaire and were eligible for PP analysis. In total, 49 (52.1% by ITT and 58.3% by PP analysis) of 94 achieved the primary endpoint after a low FODMAP diet. Overall, therefore, 251 (56.0%) of 448 patients recruited achieved the primary endpoint at either the first or second stage of the dietary intervention.

3.1 | Impact of HADS-A Scores on Response to Therapy Across Both Stages of Dietary Intervention

Baseline IBS-SSS scores were significantly lower in the group with HADS-A < 8 (267 vs. 299, $p < 0.01$) (Table 2). There was no significant difference in the numbers of patients lost to follow-up (24.3% HADS-A ≥ 8, 18.5% HADS-A < 8). Despite the difference in symptom severity on the IBS-SSS at baseline, there was no difference noted in achievement of the primary endpoint according to HADS-A scores (53.4% vs. 62.2% by ITT analysis in those with HADS-A ≥ 8 vs. HADS-A < 8, $p = 0.09$ and 70.5% vs. 76.4% by PP

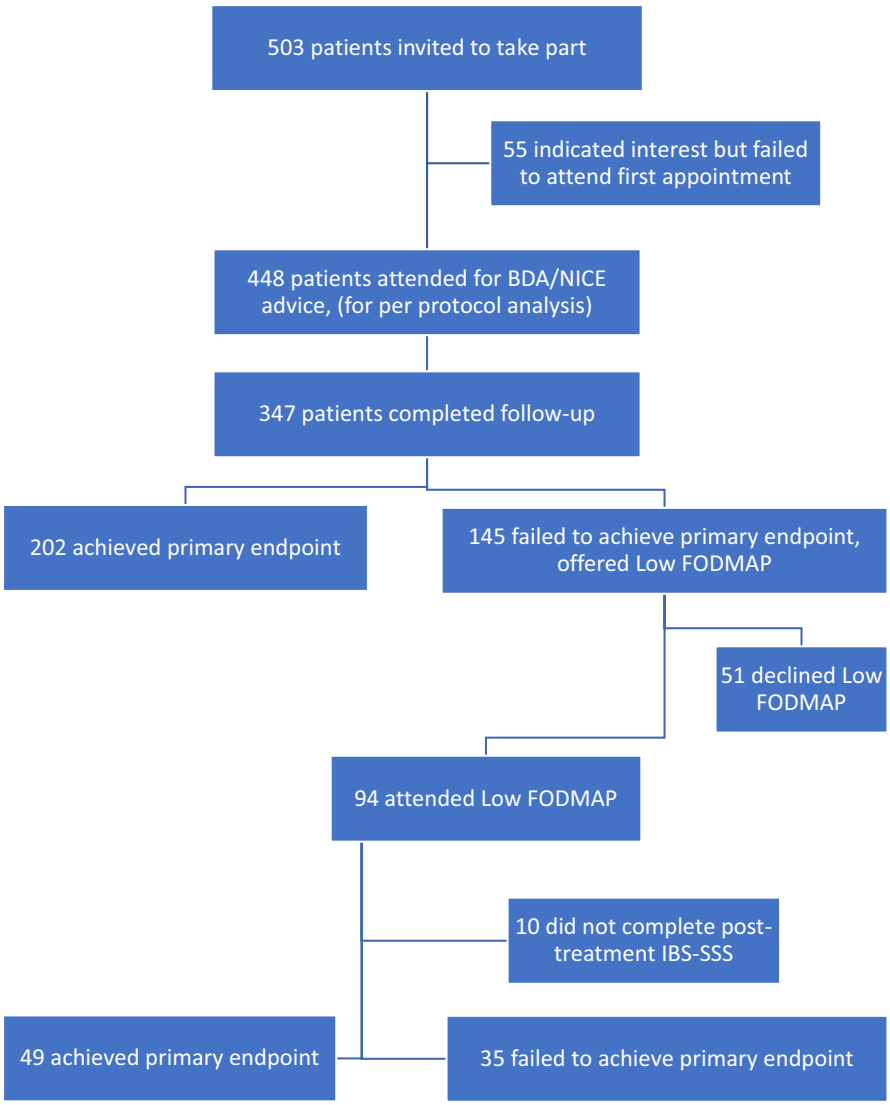

FIGURE 1 | Flow of participants through the study.

TABLE 2 | Impact of HADS-A scores on response to therapy across both stages of dietary intervention.

	HADS-D ≥ 8 ($n = 176$)	HADS-D < 8 ($n = 272$)	*p*-value
Mean IBS-SSS at baseline (SD)	324 (81)	267 (83)	< 0.01
Did not complete post-treatment IBS-SSS (%)	48/176 (27.3%)	53/272 (19.5%)	0.06
≥ 50-point decrease in IBS-SSS on ITT analysis (%)	77/176 (43.8%)	174/272 (64.0%)	< 0.01
≥ 50-point decrease in IBS-SSS on PP analysis (%)	77/128 (60.2%)	174/219 (79.5%)	< 0.01
Mean decrease in IBS-SSS from baseline (SD)	−102 (110)	−107 (81)	0.58

TABLE 3 | Impact of HADS-D scores on response to therapy across both stages of dietary intervention.

	HADS-A ≥ 8 ($n = 313$)	HADS-A < 8 ($n = 135$)	*p*-value
Mean IBS-SSS at baseline (SD)	299 (85)	267 (87)	< 0.01
Did not complete post-treatment IBS-SSS (%)	76/313 (24.3%)	25/135 (18.5%)	0.22
≥ 50-point decrease in IBS-SSS on ITT analysis (%)	167/313 (53.4%)	84/135 (62.2%)	0.09
≥ 50-point decrease in IBS-SSS on PP analysis (%)	167/237 (70.5%)	84/110 (76.4%)	0.30
Mean decrease in IBS-SSS from baseline (SD)	−106 (98)	−106 (89)	1.00

analysis in those with HADS-A ≥ 8 vs. HADS-A < 8, $p = 0.30$). In both groups, the mean decrease in IBS-SSS was 106 points.

3.2 | Impact of HADS-D Scores on Response to Therapy Across Both Stages of Dietary Intervention

Again, baseline IBS-SSS scores were significantly lower in the group with HADS-D < 8 (267 vs. 324, $p < 0.01$) (Table 3). There was no significant difference in the numbers of patients lost to follow-up (27.3% HADS-D ≥ 8, 19.5% HADS-D < 8). Patients with HADS-D ≥ 8 were significantly less likely to achieve the primary endpoint compared with those with HADS-D < 8 (43.8% vs. 64.0% by ITT analysis, $p < 0.01$ and 60.2% vs. 79.5% by PP analysis, $p < 0.01$). In both groups, the mean final change in IBS-SSS was similar with a reduction of 102 points in the HADS-D ≥ 8 group and 107 points in the HADS-D < 8 group ($p = 0.58$).

3.3 | Impact of Severity of IBS Symptoms and HADS Scores on Response to Therapy Across Both Stages of the Dietary Intervention

When the impact of IBS symptom severity and HADS scores were considered together, among those with mild or moderate IBS symptoms and HADS-D scores < 8, significantly superior response rates were observed compared with those with HADS-D scores ≥ 8 (80.0% vs. 12.5% by ITT analysis, $p < 0.01$ and 88.9% vs. 25.0% by PP analysis for mild, $p < 0.01$ and 68.5% vs. 34.6% by ITT analysis, $p < 0.01$ and 85.6% vs. 48.6% by PP analysis for moderate, $p < 0.01$, respectively) (Table 4). However, similar response rates were seen in patients with severe symptoms, regardless of HADS-A or HADS-D scores. In terms of IBS-SSS scores, the mean decrease was significantly greater in those with moderate IBS symptoms and HADS-D scores < 8, compared with those with HADS-D scores ≥ 8 (−112 vs. −60, $p < 0.01$). There were no other significant differences. There was no significant difference in IBS-SSS scores in the group who were lost to follow-up (295, SD 83) compared with those who attended for review (288, SD 159) ($p = 0.67$).

3.4 | Impact of HADS Scores on Response to Specific Dietary Therapy

When the impact of HADS scores on response to BDA/NICE-approved dietary advice or low FODMAP diet was examined, those with HADS-D scores < 8 were more likely to respond to BDA/NICE-approved dietary advice compared with those with HADS-D scores ≥ 8 (67.6% vs. 42.2%, $p < 0.01$) (Table 5), but there was no difference in response to BDA/NICE-approved dietary advice according to HADS-A scores. The mean decrease in IBS-SSS was also greater in those with HADS-D scores < 8 (−92 vs. −70, $p = 0.041$). There was no significant impact of HADS-A or HADS-D scores on response to a low FODMAP diet, although rates were generally higher in those with HADS-A scores or HADS-D scores < 8.

4 | Discussion

The heterogeneity in clinical presentations with IBS, even when patients are classified according to predominant bowel habit, and the broad array of treatment modalities for the condition, including antispasmodics, gut–brain neuromodulators, antibiotics, exclusion diets or dietary supplementation present a significant challenge to the clinician in trying to personalise management and match the right treatment to the right patient. Therefore, it is necessary that evidence exists to guide therapeutic choices based on readily identifiable disease phenotypes. In recent years, the bi-directional model of gut–brain interaction has been broadly accepted and, as this relates to IBS, it is proposed that abdominal symptoms can influence mood and that, equally, psychological factors may mediate physiological parameters such as sensory thresholds and motor function, via vagal and sympathetic mechanisms [20]. Although a large amount of data exists examining the epidemiology and proposed mechanisms of the interaction between IBS and psychological disorders, very little is understood about how this might mediate or moderate response to treatments, which is perhaps the most pertinent question for clinicians.

TABLE 4 | Impact of IBS symptom severity and HADS scores on response to therapy across both stages of dietary intervention.

	≥50-point decrease in IBS-SSS (ITT)						
	All participants (*n* = 448)	**HADS-A ≥ 8 (*n* = 313)**	**HADS-A < 8 (*n* = 135)**	***p*-value**	**HADS-D ≥ 8 (*n* = 176)**	**HADS-D < 8 (*n* = 272)**	***p*-value**
Mild (*n* = 48)	33/48 (68.8%)	13/24 (54.2%)	20/24 (83.3%)	0.06	1/8 (12.5%)	32/40 (80.0%)	< 0.01
Moderate (*n* = 182)	107/182 (58.8%)	70/125 (56.0%)	37/57 (64.9%)	0.33	18/52 (34.6%)	89/130 (68.5%)	< 0.01
Severe (*n* = 218)	111/218 (50.9%)	84/164 (51.2%)	27/54 (50.0%)	1.00	58/116 (50.0%)	53/102 (52.0%)	0.79
	≥50-point decrease in IBS-SSS (PP)						
	All participants (*n* = 347)	**HADS-A ≥ 8 (*n* = 237)**	**HADS-A < 8 (*n* = 110)**	***p*-value**	**HADS-D ≥ 8 (*n* = 128)**	**HADS-D < 8 (*n* = 219)**	***p*-value**
Mild (*n* = 40)	33/40 (82.5%)	13/18 (72.2%)	20/22 (90.9%)	0.21	1/4 (25.0%)	32/36 (88.9%)	< 0.01
Moderate (*n* = 141)	107/141 (75.9%)	70/94 (74.5%)	37/47 (78.7%)	0.67	18/37 (48.6%)	89/104 (85.6%)	< 0.01
Severe (*n* = 166)	111/166 (66.9%)	84/125 (67.2%)	27/41 (65.9%)	1.00	58/87 (66.7%)	53/79 (67.1%)	1.00
	Lost to follow-up						
	All participants (*n* = 448)	**HADS-A ≥ 8 (*n* = 313)**	**HADS-A < 8 (*n* = 135)**	***p*-value**	**HADS-D ≥ 8 (*n* = 176)**	**HADS-D < 8 (*n* = 272)**	***p*-value**
Mild (*n* = 48)	8/48 (16.7%)	6/24 (25.0%)	2/24 (8.3%)	0.24	4/8 (50.0%)	4/40 (10.0%)	0.01
Moderate (*n* = 182)	41/182 (22.5%)	31/125 (24.8%)	10/57 (17.5%)	0.34	15/52 (28.8%)	26/130 (20.0%)	0.24
Severe (*n* = 218)	52/218 (23.9%)	39/164 (23.8%)	13/54 (24.1%)	1.00	29/116 (25.0%)	23/102 (22.5%)	0.75
	Mean decrease in IBS-SSS from baseline (SD)						
	All participants (*n* = 448)	**HADS-A ≥ 8 (*n* = 313)**	**HADS-A < 8 (*n* = 135)**	***p*-value**	**HADS-D ≥ 8 (*n* = 176)**	**HADS-D < 8 (*n* = 272)**	***p*-value**
Mild (*n* = 48)	−76 (45)	−78 (44)	−71 (46)	0.63	−45 (57)	−79 (42)	0.15
Moderate (*n* = 182)	−98 (83)	−89 (79)	−116 (89)	0.07	−60 (98)	−112 (73)	< 0.01
Severe (*n* = 218)	−120 (110)	−125 (112)	−105 (101)	0.31	−125 (119)	−114 (101)	0.52

In this study, we present data assessing the effectiveness of a two-stage dietary intervention for patients with IBS-D or IBS-M according to the presence or absence of symptoms of anxiety or depression at baseline, assessed using the HADS questionnaire. Although HADS-A scores of ≥ 8 are very common in patients with IBS, there appeared to be little overall impact noted on disease severity or response to treatment. They did have higher mean IBS-SSS scores but were no more likely to be categorised as having severe than mild-to-moderate symptoms. Their response to dietary therapies was no different, when compared with those with lower scores, whether measured by the primary endpoint of this study, a 50-point decrease in IBS-SSS, or mean change in IBS-SSS, which was the same regardless of HADS-A scores. Similarly, when HADS-A status and severity were taken together, this did not predict response to therapy. However, in the context of this study set in secondary care, there is likely a selection bias as patients with mild symptoms are more likely to be managed in a primary care setting and, perhaps, may be less motivated to follow through on dietary advice and attend for subsequent follow-up.

Individuals with HADS-D scores of ≥ 8 were less frequent in this cohort and perhaps represent a more distinct subgroup of patients who are more likely to be female and older and significantly more likely to have severe symptomatology. Those with mild or moderate symptoms with HADS-D scores of ≥ 8 were less likely to respond to dietary therapy, whether measured by the primary endpoint of this study or mean change in IBS-SSS. However, in the group of patients with higher HADS-D scores and severe symptoms, which practising clinicians will recognise as a major component of the IBS workload in secondary care, a good response to therapy was seen, according to both the primary endpoint and the mean change in IBS-SSS. In this severe group, therefore, there was no difference in response to dietary

TABLE 5 | Impact of HADS scores on response to specific dietary therapy.

		All participants	HADS-A ≥ 8	HADS-A < 8	*p*-value	HADS-D ≥ 8	HADS-D < 8	*p*-value
BDA/NICE-approved dietary guidance	≥ 50-point decrease in IBS-SSS (PP)	202/347 (58.2%)	134/237 (56.5%)	68/110 (61.8%)	0.41	54/128 (42.2%)	148/219 (67.6%)	< 0.01
	Mean decrease in IBS-SSS from baseline (SD)	−85 (95)	−82 (99)	−87 (91)	0.65	−70 (115)	−92 (84)	0.04
Low FODMAP diet	≥ 50-point decrease in IBS-SSS (PP)	49/84 (58.3%)	33/58 (56.9%)	16/26 (61.5%)	0.81	23/43 (53.5%)	26/41 (63.4%)	0.38
	Mean decrease in IBS-SSS from baseline (SD)	−89 (99)	−91 (103)	−86 (91)	0.83	−93 (108)	−86 (89)	0.75

therapy based on HADS-D score. It may be that, given that loss to follow-up rates were lower in the group with HADS-D scores of ≥ 8 and severe IBS symptoms, compared with those mild IBS symptoms who were very much a minority in this cohort, that severity of the symptoms of IBS motivates good adherence to treatment. Given there was no difference in mean IBS-SSS scores between those who attended follow-up and those who did not then, at the very least, severity of symptoms does not appear to dissuade patients from engaging with dietary management. This is in and of itself notable, as depressive symptoms are associated with poor adherence across various health behaviours, which has been associated with increased mortality [21, 22].

When separated into their individual components, response to BDA/NICE-approved dietary advice or a low FODMAP diet was not significantly different according to HADS-A scores. This is particularly relevant as van Tilburg et al. reported that anxiety, ahead of other psychological comorbidities, had the worst effect on IBS symptoms through catastrophizing, as well as somatization [23]. Regarding higher HADS-D scores, there was a significantly lower response rate to the two-stage intervention, overall, but when separated into their individual components an interesting divergence was seen where response rates after BDA/NICE-approved dietary advice was inferior in the group with higher HADS-D scores, whereas no difference was seen in response to a low FODMAP diet as second-line therapy according to HADS-D score. This may relate to a lack of power, given only 94 patients commenced a low FODMAP diet. The response among those with severe symptoms is especially encouraging, as is the fact that even though those with abnormal anxiety or depression scores were more likely to have severe symptoms, they were no more likely to discontinue treatment.

There is little in the literature to infer how mood may influence response to treatment in IBS. A prospective RCT of 431 patients with IBS looking at cognitive behavioural therapy (CBT) or tricyclic antidepressants showed significantly inferior response rates to desipramine for those with more severe compared with moderate symptoms [12]. This was also suggested by a Rome foundation outcomes expert working group [24]. Another study suggested that both IBS symptoms and mood symptoms in patients with mild to moderate anxiety and/or depression on the HADS both responded well to combination probiotic therapy, which was accompanied by reduced IBS-SSS, HADS-D and HADS-A scores, and tumour necrosis factor (TNF)-α levels [25]. The authors of this study proposed that the stress response may be the major driver of IBS symptoms, based on the time course of the beneficial effect of combination therapy on the IBS symptoms, which concluded when treatment ended, whereas the time course of the effects on anxiety and depression paralleled an anti-inflammatory effect by reducing circulating levels of TNF-α over a longer period. In the ATLANTIS trial of low-dose amitriptyline, a tricyclic antidepressant commonly used for mood disorders for IBS as a second-line treatment in primary care, with a very similar patient group to ours, although larger treatment effects were noted in patients with lower baseline HADS-A scores, there was no effect of low-dose amitriptyline on somatoform symptom-reporting scores, or anxiety or depression scores during 6 months of follow-up [13]. This, again, illustrates the complexity of bi-directional gut-brain effects in IBS.

It would have been interesting in our study to note whether dietary treatments for IBS could influence HADS-A or HADS-D scores but, unfortunately, we did not collect those data. Conversely however, while it did not report on baseline HADS-A and HADS-D scores as predictors of response, a recent pilot study on the acceptability of a Mediterranean diet in IBS identified a significant improvement in HADS-A and HADS-D scores after 6 weeks of dietary treatment compared with placebo [26]. Notably, however, patients with IBS with constipation were significantly overrepresented in this group and it may be difficult to know whether this was a true effect or a manifestation of symptom relief due to increasing dietary fibre intake in constipated patients. In another study, following infusion of intragastric FODMAPs in a group of IBS patients compared with healthy controls with similar psychological symptom profiles found that, glucose induced significantly more fatigue and that fructans increased anger and sadness scores [27]. A very pertinent question raised by our study is whether IBS interventions might be able to work synergistically. For example, considering whether interventions such as CBT, which may have impact across both IBS and psychological symptom domains, can enhance the effectiveness of dietary treatments. Doing so may allow for ever more personalised, and hopefully efficacious, means of treating patients with IBS.

Although the two-stage dietary intervention reported here compares favourably with first-line drugs, such as antispasmodics, and second-line treatment with tricyclic antidepressants or selective serotonin reuptake inhibitors [28, 29], there are several other limitations to the study. For instance, the use of HADS, which focuses more on the emotional aspects of anxiety and depression, and does not contain items that measure somatic symptoms, has been controversial in studies in IBS, with some favouring the use of the GAD-7 for anxiety and the PHQ-9 for depression [30]. Nevertheless, the HADS questionnaire has been used in countless studies in IBS.

The dropout rate, and particularly the attrition of patients between the first and second stages of dietary advice, was higher than anticipated. We feel this may reflect adjustments made to the IBS service in the light of the Coronavirus pandemic, as we were no longer able to offer in-person group or one-on-one sessions and had to provide these virtually. This may also have influenced response to the interventions. Equally, this may have had an influence on the prevalence of abnormal anxiety and depression scores during the study period, with estimates suggesting an additional 53 million cases of major depressive disorder and 76 million cases of anxiety disorders were diagnosed worldwide during the pandemic [31]. Another weakness is that this study recruited patients attending secondary care and, therefore, may not be generalisable to a primary care setting. There may be an implicit selection bias in this, in terms of symptom severity and, possibly, psychological characteristics. However, accepting that most patients with IBS will not access secondary care and that there is a significant shift towards delivering care away from the hospital and closer to the patient's home in many western countries, we feel there is merit in proving feasibility of delivery of a basic first-line dietary intervention at the community level, with the more complex low FODMAP diet reserved for patients whose symptoms are refractory to this approach. We were unable to provide meals for patients undergoing the low FODMAP diet. We contend that in a pragmatic sense our study is a far more realistic representation of how such an intervention is delivered to most people in clinical practice. The study design was relatively complex, with a first and second-stage approach to dietary therapy. However, we feel this speaks to a model that is of greatest clinical utility for a problem affecting billions of people worldwide. This then feeds into a pathway of escalation to highly trained specialist dietitians attached to a multidisciplinary team for those who fail to respond, which is both desirable and more sustainable. Both interventions come without significant adverse events or toxicity and can be delivered without difficulty.

Our study highlights that understanding the psychological profile of patients may be an important factor in predicting response to dietary interventions, with symptoms of depression being of particular importance. It also emphasises that dietary treatments remain very useful in the management in IBS, with very acceptable response rates even in the key group of patients with psychological comorbidities, in whom often severe gastrointestinal symptomatology is present. Further studies are needed to compare the effectiveness of other IBS interventions and combinations of interventions, based on the common psychological comorbidities that occur in a large proportion of patients and also on the impact of IBS treatments on psychological symptoms. An accumulation of such studies would make it easier for clinicians to devise efficacious, personalised multidisciplinary treatment plans for IBS patients.

Author Contributions

Anthony O'Connor: conceptualization, investigation, writing – original draft, methodology, writing – review and editing, software, formal analysis, project administration, data curation, supervision. **Sarah Gill:** methodology, formal analysis, investigation, conceptualization, supervision, resources. **Elaine Neary:** conceptualization, investigation, methodology, formal analysis, supervision, resources. **Sarah White:** conceptualization, investigation, formal analysis. **Alexander C. Ford:** conceptualization, methodology, validation, data curation, writing – review and editing.

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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