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TITLE PAGE

Title: Efficacy of a Low FODMAP Diet in Irritable Bowel Syndrome: Systematic Review and Network Meta-analysis.

Short title: Network Meta-analysis of a Low FODMAP Diet for IBS.

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Abbreviations:

BDA	British Dietetic Association
CI	confidence interval
FDA	Food and Drug Administration
FODMAP	fermentable oligosaccharides, disaccharides, and monosaccharides, and polyols
IBS	irritable bowel syndrome
IBS-C	IBS with constipation
IBS-D	IBS with diarrhoea
NICE	National Institute for Health and Care Excellence

RCT	randomised controlled trial
RR	relative risk

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ABSTRACT

Objective: A low FODMAP diet is recommended for irritable bowel syndrome (IBS), if general lifestyle and dietary advice fails. However, although the impact of a low FODMAP diet on individual IBS symptoms has been examined in some randomised controlled trials (RCTs), there has been no recent systematic assessment, and individual trials have studied numerous alternative or control interventions, meaning the best comparator is unclear. We performed a network meta-analysis addressing these uncertainties.

Design: We searched the medical literature through to 2nd April 2021 to identify RCTs of a low FODMAP diet in IBS. Efficacy was judged using dichotomous assessment of improvement in global IBS symptoms or improvement in individual IBS symptoms, including abdominal pain, abdominal bloating or distension, and bowel habit. Data were pooled using a random effects model, with efficacy reported as pooled relative risks (RRs) with 95% confidence intervals (CIs), and interventions ranked according to their P-score.

Results: We identified 13 eligible RCTs (944 patients). Based on failure to achieve an improvement in global IBS symptoms, a low FODMAP diet ranked first versus habitual diet (RR of symptoms not improving = 0.67; 95% CI 0.48-0.91, P-score = 0.99), and was superior to all other interventions. Low FODMAP diet ranked first for abdominal pain severity, abdominal bloating or distension severity, and bowel habit, although for the latter it was not superior to any other intervention. A low FODMAP diet was superior to British Dietetic Association (BDA)/National Institute for Health and Care Excellence (NICE) dietary advice for abdominal bloating or distension (RR = 0.72; 95% CI 0.55-0.94). BDA/NICE dietary advice was not superior to any other intervention in any analysis.

Conclusion: In a network analysis, low FODMAP diet ranked first for all endpoints studied. However, most trials were based in secondary or tertiary care and did not study effects of FODMAP reintroduction and personalisation on symptoms.

STUDY HIGHLIGHTS

What is already known about this subject

- Irritable bowel syndrome (IBS) is a common condition, and efficacy of most drug treatments is modest.
- Many patients with IBS report food-induced symptoms and are interested in making dietary modifications to manage symptoms.
- Management guidelines for IBS recommend a diet low in FODMAPs, if general lifestyle and dietary advice have failed.

What are the new findings

- A low FODMAP diet was ranked first for efficacy across all endpoints studied, compared with alternative interventions, including British Dietetic Association (BDA)/National Institute for Health and Care Excellence (NICE) dietary advice for people with IBS.
- A low FODMAP diet was significantly more efficacious than habitual diet for global IBS symptoms, and significantly more efficacious than BDA/NICE dietary advice for abdominal bloating or distension.
- BDA/NICE dietary advice was not superior to any of the other interventions in any of our analyses.

How might it impact on clinical practice in the foreseeable future

- The low FODMAP diet ranked first for all endpoints studied, and was superior to all alternative interventions, including BDA/NICE dietary advice, supporting recommendations for its use in current management guidelines.

- Although guidelines recommend the use a low FODMAP diet for IBS in primary care, trials conducted in this setting, and which include the FODMAP reintroduction and personalisation phases, are needed.

INTRODUCTION

Irritable bowel syndrome (IBS), characterised by abdominal pain in association with altered stool form or frequency,[1, 2] affects 4% to 10% of the general population at any point in time.[3, 4] The condition is a disorder of gut-brain interaction,[5] and is chronic with a relapsing and remitting natural history.[6] Costs to the health service and society are substantial,[7, 8] and the impact of symptoms on quality of life is considerable,[9, 10] with patients willing to accept a median 1% risk of sudden death with a hypothetical medication in return for a 99% chance of symptom cure.[11] However, efficacy of most drugs is modest,[12-15] and placebo response rates are high.[16] Even novel, more selectively targeted, therapies developed over the last 20 years produce a therapeutic gain over placebo of only 10% to 15% and are expensive.[17] As a result, many are not widely available, and when adverse events arise during post-marketing surveillance,[18-20] they are often withdrawn, or their use restricted.[21, 22]

Patients may, therefore, turn to other approaches. Over 80% of people with IBS report food-related symptoms,[23] and in one survey more than 60% of patients had made dietary changes to manage their IBS.[24] Perhaps as a result, there has been renewed interest in dietary therapies as a treatment. One of the most widely accepted approaches is a diet that is low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). FODMAPs are present in a range of dietary sources including certain fruit, vegetables, legumes, and artificial sweeteners. Unabsorbed fructose, polyols, and lactose increase small intestinal water content and indigestible fructans and galacto-oligosaccharides undergo microbial fermentation in the colon, and contribute to symptoms in some patients.[25, 26] The low FODMAP diet consists of three phases: a period of FODMAP restriction, ideally lasting 4 to 6 weeks, reintroduction of individual food items to determine tolerance to each, and personalisation to create a modified FODMAP-containing diet based

on individual tolerance to FODMAPs identified in the second phase.[27] Several randomised controlled trials (RCTs) and meta-analyses conducted over the last 10 years have shown that the first phase of the diet is efficacious for global IBS symptoms.[28-33]

In the UK, the National Institute for Health and Care Excellence (NICE) guideline for the management of IBS in primary care recommends that if symptoms persist following general lifestyle and dietary advice further dietary management, including a low FODMAP diet, is offered.[34] Limitations of the current evidence base for a low FODMAP diet in IBS, to date, include the fact that although the impact on individual IBS symptoms has been examined in some RCTs, there has been no recent systematic assessment, and the numerous different types of alternative or control interventions studied. These have included inactive controls such as habitual diet, sham dietary advice, or even a high FODMAP diet, as well as alternative dietary advice for IBS, such as that from the British Dietetic Association (BDA), [35] or NICE, [34] which are largely empirical in nature. Both BDA and NICE advice include eating small, regular meals, keeping hydrated, reducing intake of tea, coffee, alcohol, and carbonated fluids, and limiting fruit intake, and could be viewed as an active dietary intervention. However, there have been no RCTs of this approach versus habitual diet or a sham dietary intervention, and establishing its efficacy is crucial for addressing concerns about design bias in dietary trials.[36]

We conducted a network meta-analysis to estimate the efficacy of a low FODMAP diet in IBS, as well as the relative efficacy of the different comparators studied, for both global and individual IBS symptoms. Network meta-analysis allows indirect, as well as direct, comparisons to be made across different RCTs, increasing the number of participants' data available for analysis, an advantage over published conventional pairwise meta-analyses. Importantly, it also allows a credible ranking system of the efficacy of different comparators to be developed, even in the absence of trials making direct comparisons. This may assist in

developing a more robust design for future RCTs of a low FODMAP diet, in terms of which comparator should be selected to prevent overestimating its efficacy. It also allows the relative efficacy of alternative dietary advice to be examined versus “inactive” control interventions.

METHODS

Search Strategy and Selection Criteria

We searched MEDLINE (1946 to 2nd April 2021), EMBASE and EMBASE Classic (1947 to 2nd April 2021), and the Cochrane central register of controlled trials. In addition, we searched clinicaltrials.gov for unpublished trials or supplementary data for potentially eligible RCTs. We hand-searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2001 and 2021 to identify trials published only in abstract form. Finally, we used bibliographies of all obtained articles to perform a recursive search.

RCTs examining the effect of a low FODMAP diet in adults (≥18 years) with IBS of any subtype were eligible (Supplementary Table 1). Trials had to compare a low FODMAP diet with an alternative intervention. This could consist of any of habitual diet, sham dietary advice, a high FODMAP diet, or alternative dietary advice, such as that for people with IBS from the BDA or NICE.[34, 35] Given the overlap between the latter two, we classed these as a single intervention. The first period of cross-over RCTs were eligible if they provided efficacy data prior to cross-over. We considered definitions of IBS that included either a clinician's opinion, or those that met specific symptom-based criteria, for example the Rome criteria. We required a minimum treatment duration of 2 weeks.

Two investigators (CJB and ACF) conducted the literature search, independently from each other. We identified studies on IBS with the terms: *irritable bowel syndrome* or *functional diseases, colon* (both as medical subject heading and free text terms), or *IBS*, *spastic colon*, *irritable colon*, or *functional* adj5 *bowel* (as free text terms). We combined these using the set operator AND with studies identified with the terms: *fructan$*, *FODMAP$*, or *fructooligosaccharide* (as free text terms). There were no language

restrictions. Two investigators (CJB and ACF) evaluated all abstracts identified by the search for eligibility, again independently from each other. We obtained all potentially relevant papers and evaluated them in more detail, using pre-designed forms, to assess eligibility independently and according to the pre-defined criteria. We translated foreign language papers, where required. We resolved disagreements between investigators (CJB and ACF) by discussion.

Outcome Assessment

We assessed the efficacy of a low FODMAP diet in IBS, compared with the various alternative interventions, in terms of failure to respond to therapy, according to several endpoints of interest reported below. Other outcomes assessed included adverse events (total numbers of adverse events, as well as adverse events leading to study withdrawal, and individual adverse events), if reported.

Data Extraction

Two investigators (CJB and ACF) extracted all data independently onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA, USA) as dichotomous outcomes (response or no response to therapy). We assessed efficacy according to the proportion of patients failing to achieve an improvement in the following: a) global symptoms of IBS; b) abdominal pain severity; c) abdominal bloating or distension severity; and d) bowel habit. Where studies reported a dichotomous assessment of response to therapy according to these endpoints, for example a 50-point decrease in the IBS-SSS or a 30% improvement in abdominal pain severity on the IBS-SSS (approximating Food and Drug Administration (FDA)-recommended endpoints in drug trials in IBS), we extracted data from the article itself. Where studies reported mean individual symptom severity scores at baseline

together with follow-up mean symptom severity scores and standard deviation for these endpoints for each intervention arm, we imputed dichotomous responder and non-responder data using methodology previously described by Furukawa *et al*.[37, 38] As an example, for a 30% improvement in abdominal pain severity on the IBS-SSS, this would be derived from the formula number of participants in each treatment arm at final follow-up x normal standard distribution. The latter corresponds to (70% of the baseline mean score – follow-up mean score) / follow-up standard deviation. We contacted first and senior authors of studies to provide additional data for individual trials, where required.

We also extracted the following data for each trial, where available: country of origin, setting (primary, secondary, or tertiary care), proportion of female patients, diagnostic criteria used to define IBS, and proportion of patients with IBS according to subtype. We also recorded the duration of follow-up and mode of delivery of the low FODMAP diet and the alternative intervention, in terms of the intervention itself and the length of the initial consultation, where reported. We extracted data as intention-to-treat analyses, with dropouts assumed to be treatment failures (i.e., no response to a low FODMAP diet or the comparator), wherever trial reporting allowed. If this was not clear from the original article, we performed an analysis on all patients with reported evaluable data.

Quality Assessment and Risk of Bias

We used the Cochrane risk of bias tool to assess this at the study level.[39] Two investigators (CJB and ACF) performed this independently; we resolved disagreements by discussion. We recorded the method used to generate the randomisation schedule and conceal treatment allocation, as well as whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

We performed a network meta-analysis using the frequentist model, with the statistical package "netmeta" (version 0.9-0, https://cran.r-project.org/web/packages/netmeta/index.html) in R (version 4.0.2). We reported this according to the PRISMA extension statement for network meta-analyses,[40] to explore direct and indirect treatment comparisons of the efficacy and safety of each intervention. Network meta-analysis results usually give a more precise estimate, compared with results from standard, pairwise analyses,[41, 42] and can rank interventions to inform clinical decisions.[43]

We examined the symmetry and geometry of the evidence by producing a network plot with node size corresponding to number of study subjects, and connection size corresponding to number of studies. We produced comparison adjusted funnel plots to explore publication bias or other small study effects, for all available comparisons, using Stata version 16 (Stata Corp., College Station, TX, USA). This is a scatterplot of effect size versus precision, measured via the inverse of the standard error. Symmetry around the effect estimate line indicates absence of publication bias, or small study effects.[44] We produced a pooled relative risk (RR) with 95% confidence intervals (CIs) to summarise effect of each comparison tested, using a random effects model as a conservative estimate. We used a RR of failure to achieve each of the endpoints of interest, where if the RR was less than 1 and the 95% CI did not cross 1, there was a significant benefit of one intervention over another. This approach is the most stable, compared with RR of improvement, or using the odds ratio, for some meta-analyses.[45] In each RCT, direct comparisons were made between a low FODMAP diet and a single comparator, but there were no direct comparisons made between any of the alternative interventions themselves, meaning that there was insufficient direct

evidence to perform consistency modelling to check the correlation between direct and indirect evidence across the network.[46]

Many meta-analyses use the I^2 statistic to measure heterogeneity, which ranges between 0% and 100%.[47] This statistic is easy to interpret and does not vary with the number of studies. However, the I^2 value can increase with the number of patients included in the meta-analysis.[48] We therefore assessed global statistical heterogeneity across all comparisons using the τ^2 measure from the "netmeta" statistical package. Estimates of τ^2 of approximately 0.04, 0.16, and 0.36 are considered to represent a low, moderate, and high degree of heterogeneity, respectively.[49]

We ranked both the low FODMAP diet and all comparators studied according to their P-score, which is a value between 0 and 1. P-scores are based solely on the point estimates and standard errors of the network estimates, and measure the mean extent of certainty that one intervention is better than another, averaged over all competing interventions.[50] Higher scores indicate a greater probability of the intervention being ranked as best,[50] but the magnitude of the P-score should be considered, as well as the treatment rank. As the mean value of the P-score is always 0.5 if individual interventions cluster around this value they are likely to be of similar efficacy. However, when interpreting the results, it is also important to take the RR and corresponding 95% CI for each comparison into account, rather than relying on rankings alone.[51] In our primary analyses, we pooled data for the risk of being symptomatic at the final point of follow-up in each study for all included RCTs using an intention-to-treat analysis, but we also performed *a priori* analyses restricted to trials that used identical endpoints to judge efficacy, and trials that recruited patients with IBS with diarrhoea (IBS-D), or excluded those with IBS with constipation (IBS-C).

RESULTS

The search strategy generated 1231 citations, 79 of which appeared relevant and were retrieved for further assessment (Supplementary Figure 1). Of these, we excluded 66 that did not fulfil eligibility criteria, leaving 13 eligible articles,[28, 29, 33, 52-61] which included 944 patients, 472 of whom were allocated to a low FODMAP diet. Twelve RCTs evaluated low FODMAP dietary advice,[28, 33, 52-61] and one RCT evaluated a low FODMAP diet in which participants were provided with the majority of food to be consumed and advised about fluid choices throughout the duration of the intervention.[29] In terms of the alternative intervention, 237 patients received BDA/NICE dietary advice for IBS in five RCTs,[33, 52-55] 106 were allocated to habitual diet in four RCTs,[28, 29, 56, 57] 76 were randomised to sham dietary advice in two trials,[58, 59] 33 were allocated to alternative brief dietary advice in one RCT,[60] and 20 received a high FODMAP diet in one trial (Supplementary Table 2).[61] Agreement between investigators for trial eligibility was excellent (kappa statistic = 0.82). Seven trials recruited only patients with IBS-D or excluded those with IBS-C specifically.[28, 33, 53-55, 58, 59] Detailed characteristics of individual RCTs are provided in Table 1.

All trials were published in full. We obtained extra data from the investigators of seven RCTs.[53, 55-60] Risk of bias for all included trials is reported in Supplementary Table 3. No RCT was at low risk of bias across all domains, although nine trials were low risk of bias across all domains other than double blinding.[28, 52, 54-59, 61] Dietary trials are inherently difficult to blind, but two trials stated that investigators were blinded to treatment allocation,[33, 55] and eight that patients were blinded.[29, 52-54, 58-61] Endpoints used, or imputed, in each trial are provided in Supplementary Table 4. Adverse events were not reported in sufficient detail in most trials to allow any meaningful pooling of data.

Table 1. Characteristics of Randomised Controlled Trials of a Low FODMAP Diet for IBS.

Study	Country and setting	Duration	Details of low FODMAP diet and number of patients	Details of comparator and number of patients	Number (%) female	Diagnostic criteria used for IBS, and number (%) with each subtype
Bohn 2015 [52]	Sweden, secondary and tertiary care	4 weeks	38 patients assigned to a low FODMAP diet, with dietary advice from a dietitian and provision of written information	37 patients assigned to BDA/NICE diet, with dietary advice from a dietitian and provision of written information	61 (81.3%)	Rome III, 22 (29.3%) IBS-C, 18 (24.0%) IBS-D, 35 (46.7%) IBS-M
Eswaran 2016 [33]	USA, tertiary care	4 weeks	50 patients assigned to a low FODMAP diet, with dietary advice from a dietitian and provision of teaching materials	42 patients assigned to NICE diet, with dietary advice from a dietitian and provision of teaching materials	65 (70.7%)	Rome III, 92 (100%) IBS-D
Zahedi 2018 [53]	Iran, secondary care	6 weeks	55 patients assigned to a low FODMAP diet, with dietary advice from a dietitian during a 45-minute appointment and provision of written information	55 patients assigned to BDA diet, with dietary advice from a dietitian during a 45-minute appointment	51 (50.5%)	Rome III, 110 (100%) IBS-D

Goyal 2021 [54]	India, secondary care	4 weeks	52 patients assigned to a low FODMAP diet, with dietary advice from a dietitian and provision of written information	49 patients assigned to BDA/NICE diet, with dietary advice from a dietitian and provision of written information	42 (41.6%)	Rome IV, 101 (100%) IBS-D
Zhang 2021 [55]	China, tertiary care	3 weeks	54 patients assigned to a low FODMAP diet, with dietary advice from a dietitian during a 20-minute appointment and a menu plan to follow	54 patients assigned to BDA/NICE diet, with dietary advice from a dietitian during a 20-minute appointment and a menu plan to follow	51 (47.2%)	Rome III, 108 (100%) IBS-D
Staudacher 2012 [28]	UK, tertiary care	4 weeks	19 patients assigned to a low FODMAP diet, with dietary advice from a dietitian during a 45-minute appointment	22 patients advised to continue with their habitual diet by a dietitian during a 45-minute appointment	27 (65.9%)	Rome III, subtype not stated but excluded patients with IBS-C
Halmos 2014 [29]	Australia, unclear	3 weeks	13 patients assigned to a low FODMAP diet, with almost all food provided as frozen complete meals, but additional food lists provided to enable purchase of additional low FODMAP foods	17 patients assigned to a typical Australian diet, with almost all food provided as frozen complete meals, but additional food lists provided to enable purchase of additional FODMAP-containing foods	21 (70.0%)	Rome III, 13 (43.3%) IBS-C, 10 (33.3%) IBS-D, 5 (16.7%) IBS-M

Pedersen 2014 [56]	Denmark, tertiary care	6 weeks	42 patients assigned to a low FODMAP diet, with dietary advice from a dietitian during a 1-hour appointment and additional food lists provided	40 patients continued with their habitual diet	63 (76.8%)	Rome III, 12 (14.6%) IBS-C, 37 (45.1%) IBS-D, 28 (34.1%) IBS-M
Harvie 2017 [57]	New Zealand, primary, secondary, and tertiary care	3 months	23 patients assigned to a low FODMAP diet, with dietary advice from a dietitian during a 1-hour appointment	27 patients continued with their habitual diet	43 (86.0%)	Rome III, 5 (10.0%) IBS-C, 32 (64.0%) IBS-D, 14 (28.0%) IBS-M
Staudacher 2017 [58]	UK, tertiary care	4 weeks	51 patients assigned to a low FODMAP diet, with dietary advice from a dietitian of 10 minutes duration, based on provided food lists	53 patients assigned to a sham dietary intervention, with dietary advice from a dietitian of 10 minutes duration, based on provided food lists	70 (67.3%)	Rome III, 69 (66.3%) IBS-D, 24 (23.1%) IBS-M, 11 (10.6%) IBS-U
Wilson 2020 [59]	UK, tertiary care	4 weeks	22 patients assigned to a low FODMAP diet, with dietary advice from a dietitian during a 1-hour appointment and provision of written information	23 patients assigned to a sham dietary intervention, with dietary advice from a dietitian during a 15 to 25-minute appointment and provision of written information	25 (55.6%)	Rome III, 45 (66.7%) IBS-D, patients with IBS-C were excluded

Patcharatrakul 2019 [60]	Thailand, secondary care	4 weeks	33 patients assigned to a low FODMAP diet, with dietary advice from a gastroenterologist during a 30-minute appointment, an example food menu, and provision of written information	33 patients assigned to dietary advice from a gastroenterologist during a 5-minute appointment	47 (75.8%)	Rome III, subtype not stated
McIntosh 2016 [61]	Canada, tertiary care	3 weeks	20 patients assigned to a low FODMAP diet, with dietary advice from a dietitian during a 30 to 60-minute appointment, sample food menus, and provision of written information	20 patients assigned to a high FODMAP diet, with dietary advice from a dietitian during a 30 to 60-minute appointment, sample food menus, and provision of written information	32 (86.5%)	Rome III, 2 (5.0%) IBS-C, 10 (25.0%) IBS-D, 23 (57.5%) IBS-M, 1 (2.5%) IBS-U

Global IBS Symptoms

Twelve RCTs provided extractable dichotomous data,[28, 29, 33, 52-59, 61] and data were imputed for another study,[60] meaning that all 13 trials contributed to this analysis. The network plot is provided in Supplementary Figure 2. When data were pooled, there was no heterogeneity ($\tau^2 = 0$), and the funnel plot appeared symmetrical (Supplementary Figure 3). However, there was evidence of funnel plot asymmetry when pooling pairwise data, suggesting publication bias or other small study effects (Egger test, P = 0.043) (Supplementary Figure 4). Compared with habitual diet, a low FODMAP diet was ranked first (RR of global IBS symptoms not improving = 0.67; 95% CI 0.48 to 0.91, P-score 0.99) (Figure 1). This means that the probability of a low FODMAP diet being the most efficacious when all interventions were compared with each other was 99%. Among alternative interventions, compared with habitual diet, BDA/NICE dietary advice was ranked second (RR = 0.82; 95% CI 0.57-1.18, P-score 0.71) and high FODMAP diet last (P-score 0.10). Low FODMAP diet was superior to all other interventions, including BDA/NICE dietary advice (Table 2). None of the alternative interventions was superior to habitual diet, or any of the other alternative interventions.

There were seven RCTs that used a 50-point decrease in the IBS-SSS to define response.[52-57, 61] When we restricted the analysis to these studies, low FODMAP diet was still ranked first, although it was no more efficacious than habitual diet (RR = 0.76; 95% CI 0.53 to 1.11, P-score 0.97) (Supplementary Figure 5). However, it was more efficacious than both BDA/NICE dietary advice and a high FODMAP diet (Supplementary Table 5). There were no other significant differences. When we restricted the analysis to seven trials that recruited only patients with IBS-D, or excluded those with IBS-C specifically,[28, 33, 53-55, 58, 59] low FODMAP diet again ranked first for global IBS symptoms (RR = 0.41; 95% CI 0.20 to 0.82, P-score 0.99) (Supplementary Figure 6) and was superior to all alternative

Table 2. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve an Improvement in Global IBS Symptoms.

Low FODMAP diet					
0.81 (0.67; 0.97)	**BDA/NICE dietary advice**				
0.70 (0.52; 0.95)	0.87 (0.61; 1.23)	**Sham dietary advice**			
0.67 (0.48; 0.91)	0.82 (0.57; 1.18)	0.95 (0.61; 1.47)	**Habitual diet**		
0.58 (0.38; 0.87)	0.71 (0.45; 1.12)	0.82 (0.49; 1.37)	0.87 (0.52; 1.46)	**Alternative dietary advice**	
0.44 (0.23; 0.83)	0.54 (0.28; 1.05)	0.62 (0.31; 1.26)	0.66 (0.32; 1.34)	0.76 (0.36; 1.62)	**High FODMAP diet**

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The intervention in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes shaded green denote a statistically significant difference.

BDA/NICE; British Dietetic Association/National Institute for Health and Care Excellence, FODMAP; fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

interventions (Supplementary Table 6). There were no significant differences between alternative interventions.

Abdominal Pain Severity

There were 12 trials reporting data on effect on abdominal pain severity,[28, 33, 52-61] recruiting 914 patients, 459 of whom received a low FODMAP diet. Five trials compared a low FODMAP diet with BDA/NICE dietary advice for IBS,[33, 52-55] three habitual diet,[28, 56, 57] two sham dietary advice,[58, 59] one alternative brief dietary advice,[60] and one high FODMAP diet.[61] The network plot is provided in Supplementary Figure 7. When data were pooled, there was moderate heterogeneity ($\tau^2 = 0.068$), and the funnel plot appeared symmetrical (Supplementary Figure 8), but again there was funnel plot asymmetry when pooling pairwise data (Egger test, P = 0.025) (Supplementary Figure 9). Compared with habitual diet, a low FODMAP diet ranked first, but it was not superior in terms of efficacy (RR of abdominal pain severity not improving = 0.72; 95% CI 0.47 to 1.10, P-score 0.92) (Figure 2). A low FODMAP diet was superior to sham dietary advice (Table 3), but there were no other significant differences.

There were nine RCTs that used an endpoint of a 30% improvement in abdominal pain severity on the IBS-SSS.[33, 52-54, 56-59, 61] Restricting the analysis to these studies, low FODMAP diet still ranked first, although again it was no more efficacious than habitual diet (RR = 0.74; 95% CI 0.43 to 1.28, P-score 0.94) (Supplementary Figure 10). However, it was more efficacious than sham dietary advice, although there were no other significant differences (Supplementary Table 7). When we restricted the analysis to seven trials that recruited only patients with IBS-D, or excluded those with IBS-C specifically,[28, 33, 53-55, 58, 59] low FODMAP diet again ranked first but was not superior to habitual diet (RR = 0.63; 95% CI 0.22 to 1.81, P-score 0.91) (Supplementary Figure 11). However, low

Table 3. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve an Improvement in Abdominal Pain Severity.

Low FODMAP diet					
0.79 (0.39; 1.59)	**Alternative dietary advice**				
0.78 (0.57; 1.06)	0.98 (0.46; 2.11)	**BDA/NICE dietary advice**			
0.72 (0.47; 1.10)	0.91 (0.40; 2.06)	0.92 (0.54; 1.57)	**Habitual diet**		
0.51 (0.30; 0.87)	0.65 (0.27; 1.56)	0.66 (0.35; 1.22)	0.71 (0.36; 1.41)	**Sham dietary advice**	
0.47 (0.20; 1.07)	0.59 (0.20; 1.74)	0.60 (0.25; 1.45)	0.65 (0.26; 1.65)	0.91 (0.34; 2.44)	**High FODMAP diet**

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The intervention in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes shaded green denote a statistically significant difference.

BDA/NICE; British Dietetic Association/National Institute for Health and Care Excellence, FODMAP; fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

FODMAP diet was again superior to sham dietary advice (Supplementary Table 8). There were no significant differences between alternative interventions.

Abdominal Bloating or Distension Severity

The same 12 RCTs, recruiting 914 patients, provided data for effect on abdominal bloating or distension severity.[28, 33, 52-61] The network plot is provided in Supplementary Figure 12. There was moderate heterogeneity ($\tau^2 = 0.058$), and the funnel plot appeared symmetrical (Supplementary Figure 13), with no evidence of funnel plot asymmetry when pooling pairwise data (Egger test, P = 0.31). Compared with habitual diet, low FODMAP diet ranked first, but it was not superior in terms of efficacy (RR of abdominal bloating or distension severity not improving = 0.71; 95% CI 0.47 to 1.06, P-score 0.82) (Figure 3). However, a low FODMAP diet was superior to BDA/NICE dietary advice (Table 4). There were no other significant differences.

There were nine RCTs that used an endpoint of a 30% improvement in abdominal distension severity on the IBS-SSS.[33, 52-54, 56-59, 61] When we restricted the analysis to these studies, low FODMAP diet still ranked first, although again it was no more efficacious than habitual diet (RR = 0.80; 95% CI 0.49 to 1.30, P-score 0.84) (Supplementary Figure 14). However, it was more efficacious than BDA/NICE dietary advice, which ranked last (Supplementary Table 9). There were no other significant differences. When we restricted the analysis to seven trials that recruited only patients with IBS-D or excluded those with IBS-C,[28, 33, 53-55, 58, 59] low FODMAP diet again ranked first but was not superior to habitual diet (RR = 0.46; 95% CI 0.18 to 1.20, P-score 0.86) (Supplementary Figure 15). However, low FODMAP diet was superior to BDA/NICE dietary advice (Supplementary Table 10). There were no significant differences between alternative interventions.

Table 4. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve an Improvement in Abdominal Bloating or Distension Severity.

Low FODMAP diet					
0.95 (0.50; 1.79)	**Alternative dietary advice**				
0.85 (0.51; 1.43)	0.90 (0.40; 2.05)	**Sham dietary advice**			
0.69 (0.36; 1.32)	0.73 (0.29; 1.81)	0.81 (0.35; 1.86)	**High FODMAP diet**		
0.72 (0.55; 0.94)	0.76 (0.38; 1.52)	0.84 (0.47; 1.52)	1.05 (0.51; 2.13)	**BDA/NICE dietary advice**	
0.71 (0.47; 1.06)	0.75 (0.35; 1.59)	0.83 (0.43; 1.60)	1.03 (0.48; 2.22)	0.98 (0.61; 1.60)	**Habitual diet**

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The intervention in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes shaded green denote a statistically significant difference.

BDA/NICE; British Dietetic Association/National Institute for Health and Care Excellence, FODMAP; fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

Improvement in Bowel Habit

Ten trials provided data on effect on improvement in bowel habit,[33, 52-59, 61] randomising 807 patients. Of these, 407 received a low FODMAP diet. Five trials compared a low FODMAP diet with BDA/NICE dietary advice for IBS,[33, 52-55] two habitual diet,[56, 57] two sham dietary advice,[58, 59] and one high FODMAP diet.[61] The network plot is provided in Supplementary Figure 16. When data were pooled, there was moderate heterogeneity ($\tau^2 = 0.071$), and the funnel plot appeared symmetrical (Supplementary Figure 17). However, there was funnel plot asymmetry when pooling pairwise data (Egger test, P = 0.0034) (Supplementary Figure 18). Compared with habitual diet, a low FODMAP diet ranked first, but again it was not superior in terms of efficacy (RR of bowel habit not improving = 0.62; 95% CI 0.37 to 1.04, P-score 0.88) (Figure 4). There were no significant differences between low FODMAP diet and any of the comparators (Table 5).

There were eight RCTs that used an endpoint of a 30% improvement in bowel habit on the IBS-SSS.[52-54, 56-59, 61] When we restricted the analysis to these studies, low FODMAP diet ranked first, although it was no more efficacious than habitual diet (RR = 0.60; 95% CI 0.31 to 1.18, P-score 0.84) (Supplementary Figure 19), or to any other alternative intervention (Supplementary Table 11). When restricting the analysis to the six trials that recruited only patients with IBS-D or excluded those with IBS-C specifically,[33, 53-55, 58, 59] a low FODMAP diet again ranked first but was not superior to sham dietary advice (RR = 0.82; 95% CI 0.51 to 1.32, P-score 0.87) (Supplementary Figure 20), and there were no significant differences between any of the other interventions (Supplementary Table 12).

Table 5. Summary Treatment Effects from the Network Meta-analysis for Failure to Achieve an Improvement in Bowel Habit.

Low FODMAP diet				
0.83 (0.55; 1.25)	**Sham dietary advice**			
0.81 (0.61; 1.07)	0.97 (0.59; 1.60)	**BDA/NICE dietary advice**		
0.73 (0.36; 1.48)	0.88 (0.39; 1.99)	0.90 (0.42; 1.93)	**High FODMAP diet**	
0.62 (0.37; 1.04)	0.75 (0.39; 1.44)	0.77 (0.43; 1.38)	0.85 (0.36; 2.03)	**Habitual diet**

Relative risk with 95% confidence intervals in parentheses. Comparisons, column versus row, should be read from left to right, and are ordered relative to their overall efficacy. The intervention in the top left position is ranked as best after the network meta-analysis of direct and indirect effects. Boxes shaded green denote a statistically significant difference.

BDA/NICE; British Dietetic Association/National Institute for Health and Care Excellence, FODMAP; fermentable oligosaccharides, disaccharides, monosaccharides, and polyols.

DISCUSSION

This is the first systematic review and network meta-analysis of a low FODMAP diet for IBS, comparing its efficacy against alternative dietary advice for IBS, such as that provided by the BDA and NICE, as well as inactive control interventions. A low FODMAP diet ranked first for global IBS symptoms, and was superior to all alternative interventions studied, including BDA/NICE dietary advice. In terms of its effects on individual symptoms a low FODMAP diet was superior to sham dietary advice for abdominal pain severity, and it was superior to BDA/NICE dietary advice for abdominal bloating or distension severity. We did not detect any significant effect of a low FODMAP diet on bowel habit when data from these trials were pooled. When we restricted the analysis to trials that used identical dichotomous endpoints to assess response to treatment, or trials excluding patients with IBS-C, results were broadly similar. Most trials did not report adverse events in detail, precluding any relevant meaningful analysis.

We undertook the literature search, eligibility assessment, and data extraction in duplicate and independently, with any discrepancies resolved by consensus. We used an intention-to-treat analysis, assuming all dropouts failed therapy, and pooled data with a random effects model, to reduce the likelihood that any beneficial effect of a low FODMAP diet in IBS, or the alternative or control interventions studied, has been overestimated. We also contacted authors of seven studies to obtain supplementary data to maximise the number of eligible RCTs in the network,[53, 55-60] and imputed dichotomous responder data using means and standard deviations according to validated methods.[37, 38] This allowed us to include global IBS symptom data from three trials, and 242 patients, that would otherwise have been excluded altogether,[53, 56, 57] as well as to study the effect of a low FODMAP diet on individual symptoms of abdominal pain severity, abdominal bloating or distension severity, and improvement in bowel habit, using endpoints that were relatively standardised

between trials, and which are closely aligned to those recommended by the FDA. This network meta-analysis, therefore, represents a considerable advance over previous pairwise meta-analyses.

There are some limitations. No trials were at low risk of bias, due to a lack of double blinding, although this is almost impossible in dietary trials, and 10 trials blinded either investigators or patients to treatment allocation. Based on quality assessment criteria intended for pharmacotherapy trials, it would be recommended the results of the network meta-analysis are interpreted with caution, as trials that do not employ double blinding tend to overestimate efficacy of the intervention studied.[62] However, it could be argued that this is not possible in dietary and other non-pharmacotherapy trials (e.g. psychological therapies). Four of the RCTs restricted recruitment to patients with IBS-D,[33, 53-55] and a further three did not recruit patients with IBS-C,[28, 58, 59] meaning the efficacy of a low FODMAP diet in those with IBS-C or IBS with a mixed stool pattern is less clear. Even though a low FODMAP diet is recommended as a dietary intervention in primary care,[34] all but one of the trials was conducted in secondary or tertiary care.[57] There was no heterogeneity in our analysis for global IBS symptoms, but moderate heterogeneity in our other analyses, which may relate to mode of delivery and nature of the interventions studied. There was also evidence of funnel plot asymmetry for all analyses, except abdominal bloating or distension severity. Despite these limitations, the results of our study are still useful for informing treatment decisions for patients and can be used in future updates of evidence-based IBS management guidelines.[17, 32, 34]

Restriction of FODMAPs is not recommended long-term, to minimise risk of nutritional inadequacy. Further, short-term alterations in the gastrointestinal microbiota have been reported, including a consistent finding of reduced abundance of Bifidobacteria.[28, 59, 63] Although the long-term consequences of these changes are unknown, reintroduction of

high FODMAP foods to tolerance is a critical phase of the low FODMAP diet in clinical practice and may curb the impacts on dietary intake and the microbiota. However, very few of the included RCTs incorporated this phase of the diet into their design, meaning that the effect of FODMAP reintroduction on IBS symptoms remains unclear. One 4-week trial comparing a low FODMAP diet with BDA/NICE dietary advice reported data at 12 weeks, after FODMAP reintroduction, and still demonstrated a significant difference in responder rates favouring a low FODMAP diet at 16 weeks.[54] Uncontrolled studies support the long-term efficacy of the diet after FODMAP reintroduction.[64, 65] However, RCTs are needed to confirm this, although it is acknowledged these are difficult to carry out, particularly with regard to blinding over longer periods of time and minimising attrition.[66] Outside of a clinical trial setting individual patients may struggle with the FODMAP restriction phase of the diet, although a real-world study demonstrated less than 10% of patients were non-adherent during this part of the intervention.[67]

Our results confirm that a low FODMAP diet is an efficacious treatment for global IBS symptoms in secondary and tertiary care. Importantly, a dietitian delivered counselling in all but one of the 12 low FODMAP dietary advice RCTs.[60] These findings support the use of a low FODMAP diet under dietetic supervision, although it is important to point out that RCTs in primary care are lacking, which is in contrast with its placement in current NICE guidance for the management of IBS.[34] The recent British Society of Gastroenterology guidelines for the management of IBS also recommend the use of a low FODMAP diet as a second-line dietary approach in those individuals who have not responded to first-line advice.[32] These guidelines stated that it was likely to be beneficial for both global IBS symptoms, and abdominal pain, based on an update of a prior systematic review and pairwise meta-analysis.[30] However, our analysis suggests that any effect on abdominal pain severity, versus alternative dietary advice or a habitual diet, is less certain.

Of note, BDA/NICE dietary advice was not superior to any of the alternative or control interventions in our analyses, and a low FODMAP diet was significantly more efficacious for both global IBS symptoms and abdominal bloating or distension severity. This contrasts with the results of individual trials themselves,[33, 52-55] and likely relates to the increased power of the meta-analysis to detect smaller, but still potentially clinically relevant, differences. Nevertheless, there were fewer patients assigned to BDA/NICE dietary advice than a low FODMAP diet and it is, perhaps, premature to dismiss this approach based on the findings of this network meta-analysis, particularly as it usually less intensive to follow than the whole-diet approach of a low FODMAP diet. Indeed, there are also safety, microbiological, and clinical capacity implications of a low FODMAP diet, which were unable to be examined as part of this meta-analysis, and which mean BDA/NICE dietary advice is still a reasonable first-line dietary approach. We believe there is still, therefore, a need for head-to-head trials of BDA/NICE dietary advice versus sham dietary advice, to assess whether the dietary modifications recommended are beneficial for patients with IBS. These trials should ideally include specific IBS subtypes as the nature of dietary changes based on BDA/NICE dietary advice are dependent on symptom profile. In terms of alternative interventions studied, a high FOMDAP diet ranked last for global IBS symptoms and abdominal pain severity, suggesting its use as a comparator is likely to overestimate efficacy of a low FODMAP diet. This is expected, given previous research showing acute challenge with individual FODMAPs provokes symptoms in IBS.[25] Habitual diet ranked last in several analyses. This is, perhaps, not surprising as this is similar to an “attention” control used in trials of psychological therapies,[68] where patients receive no treatment. There is the possibility that, in a trial designed to assess an active dietary intervention, being randomised to continue usual diet is associated with anticipation that symptoms will not improve, leading to overestimation of the efficacy of a low FODMAP diet. Both sham dietary

advice and BDA/NICE dietary advice ranked higher and should be preferred as a comparator in future RCTs. They should be made as comparable as possible with the low FODMAP diet in terms of complexity of the intervention and time spent with the dietitian.

In summary, this systematic review and network meta-analysis has demonstrated that a low FODMAP diet ranked first in all analyses, compared with five alternative interventions, in IBS in terms of efficacy. Although BDA/dietary advice ranked second for global symptoms, it was not superior to a low FODMAP diet for any of the endpoints studied, and it performed no better than the other alternative or control interventions questioning its place in IBS primary care guidelines. Of note, almost all low FODMAP dietary advice RCTs implemented a dietitian-delivered intervention, emphasising the importance of dietetic supervision. This may limit availability in a clinical practice setting. Seven trials excluded patients with IBS-C, meaning the benefit of these dietary approaches in this patient group is less clear, and only one trial examined the effect of FODMAP reintroduction on IBS symptoms. The inherent challenges of study design in trials of dietary intervention meant that the quality of the evidence, according to GRADE criteria, [69] was low for a low FODMAP diet due to risk of bias of included RCTs, as well as imprecision due to uncertainty around effects and possible publication bias, and very low for all other interventions studied. However, endpoints we used to judge efficacy approximated those recommended by the FDA. Adverse event reporting was suboptimal in most trials. In addition, even though a low FODMAP diet or BDA/NICE dietary advice are recommended for patients with IBS in primary care, and before referral to a gastroenterologist, most trials were conducted in referral populations. Further RCTs of both a low FODMAP diet and BDA/NICE dietary advice against each other, or against sham dietary advice, in primary care that are powered adequately, used FDA-recommended endpoints, examine efficacy during the FODMAP

reintroduction and personalisation phase, and report adverse events data more thoroughly are required.

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CONTRIBUTOR AND GUARANTOR INFORMATION

Guarantor: ACF is guarantor. He accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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COMPETING INTERESTS DECLARATION

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

TRANSPARENCY STATEMENT

The lead author (ACF, the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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PATIENT AND PUBLIC INVOLVEMENT STATEMENT

We did not involve patients or the public in this work. We will disseminate our findings in lay terms via the national charity for people living with digestive diseases, “Guts UK”, and the national charity for people living with IBS, the IBS Network.

DATA SHARING

No additional data available.

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FIGURES

Figure 1. Forest Plot for Failure to Achieve an Improvement in Global IBS Symptoms.

Note: The P-score is the probability of each intervention being ranked as best in the network.

Figure 2. Forest Plot for Failure to Achieve an Improvement in Abdominal Pain Severity.

Note: The P-score is the probability of each intervention being ranked as best in the network.

Figure 3. Forest Plot for Failure to Achieve an Improvement in Abdominal Bloating or Distension Severity.

Note: The P-score is the probability of each intervention being ranked as best in the network.

Figure 4. Forest Plot for Failure to Achieve an Improvement in Bowel Habit.

Note: The P-score is the probability of each intervention being ranked as best in the network.