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Systematic review: quality of trials on the symptomatic effects of the low FODMAP diet for irritable bowel syndrome

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Summary

Background: The low Fermentable Oligo-, Di- Monosaccharides, and Polyoles (FODMAP) diet is a new treatment option for irritable bowel syndrome (IBS). Experts refer to the diet as supported by high level of evidence, but an evaluation of the quality of trials is lacking.

Aim: To provide a systematic review of the quality of trials on the symptomatic effects of the low FODMAP diet for IBS.

Methods: Pubmed and EMBASE were searched for randomised controlled trials (RCTs) reporting effect of the low FODMAP diet on IBS symptoms. The quality of trials was evaluated by estimating risk of bias and assessing trial methodology.

Results: Nine RCTs were eligible, including 542 patients. The intervention period was from 2 days to 6 weeks and one trial included a 6-month follow-up. Three trials intervened by providing meals, controlling with a diet high in FODMAP content. In six trials, the intervention was instruction by a dietician and a variety of control interventions were used, all with limited established efficacy. Domains with a high risk of bias were identified for all the trials. High risk of bias dominated domains regarding blinding, with only one trial double-blinded.

Conclusions: The RCTs on the low FODMAP diet are characterized by high risk of bias. The diet has not been studied in a randomised, controlled setting for more than 6 weeks and trials examining the effect of the important reintroduction period are lacking. There is a risk that the symptomatic effects reported in the trials are driven primarily by a placebo response.

1 | INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder[1] characterised by recurrent abdominal pain in association with altered bowel movements. The pathophysiology of IBS remains unknown, but many patients report their symptoms to be associated to their diet and that specific foods cause worsening in symptoms, consequently leading them to exclude various food items from the diet.[2-4]

Treatment options of IBS are limited and merely symptomatic and include diet and lifestyle changes. Several dietetic interventions have been studied with varying results.[5] In recent years, focus has been on the low FODMAP diet. A diet low in a group of fermentable, short-chained carbohydrates: Fermentable Oligo-, Di- Monosaccharides, and Polyoles (FODMAP).

FODMAPs are poorly absorbed in the small intestine and reach the colon undigested. They cause an osmotic increase of water content in the intestines and increased gas production due to bacterial fermentation.[6] This occurs both in healthy persons[7] and in patients with IBS, where it is thought to cause symptoms due to visceral hypersensitivity and altered motility.[6,8]

A treatment course of the low FODMAP diet commences with an elimination period of 4-8 weeks, excluding or restricting foods high in FODMAPs. When symptom relief is reported, foods high in

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FODMAPs are reintroduced one by one to identify the type and amount of FODMAPs, which can be tolerated.

This relatively new diet has gained much attention and information about the diet is available on the internet in excess. Experts recommend the diet as first-line treatment for IBS[9] and refer to the diet as being supported by a high level of evidence.[10] A systematic review evaluated the effect of the low FODMAP diet for IBS.[11] The authors concluded, based on a meta-analysis that the diet can be implemented as a key treatment strategy in IBS, but evaluation of the quality of the trials was not reported. However, a critical appraisal of the quality of the data on which the evidence is based is of fundamental importance.

Therefore, the aim of this systematic review was to assess the quality of randomised controlled trials (RCT) evaluating the symptomatic effects of the low FODMAP diet as a treatment for IBS.

2 | MATERIALS AND METHODS

A systematic search of the medical literature was conducted using the databases PubMed (1970 to October 2016) and Embase (1974 to October 2016). Eligible trials included randomised, controlled trials if they reported effect of the low FODMAP diet on IBS symptoms. We included trials on patients of any age diagnosed with IBS by a physician based on clinical opinion or by symptom-based diagnostic criteria. Trials, that either used intervention by restricting FODMAPs, as instructed by a dietician or as complete meals provided for the patient, were considered eligible for inclusion. Eligibility of trials was not restricted by length of intervention period.

A search strategy was developed consisting of the following terms: "Irritable bowel syndrome" (as medical subject heading (MeSH) and free text term), "IBS" (free text term), "functional colonic disease" (free text term) and "colonic diseases, functional" (MeSH term). The search was specified to trials on the low FODMAP diet by using the operator AND with the following terms: "low fodmap diet", "fodmap diet" or "fodmap", all as free text terms. The last search was performed on 24th of October 2016. The reference lists of included articles were searched for relevant trials. Only trials in English were included. Trials only reported in abstract form were excluded.

2.1 | Trial selection

Titles and abstracts were reviewed by LRK. LRK and PB evaluated relevant papers independently according to predefined eligibility criteria. Any disagreement in selecting trials was resolved by consensus.

2.2 | Outcome assessment

Primary outcome assessed was the quality of trials on the low FODMAP diet as a treatment for IBS. The quality of trials was evaluated by estimating risk of bias and assessing the general methodology.

2.3 | Data extraction

PB and LRK extracted data from included papers. Data on study design, number of participants included, intervention, control group, length of study, length of follow-up, definition of symptom improvement, random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, choice of control group and objective evaluation of data was extracted.

2.4 | Risk of bias assessment

The risk of bias was assessed by the Cochrane collaborations tool.[12] LRK and PB independently reviewed the trials for the domains random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). Two types of "other bias" included in the assessment were prespecified: choice of control group (bias in design) and objective evaluation of data (interpretive bias[13]).

2.5 | Statistics

A meta-analysis was not applicable.

3 | RESULTS

The search strategy generated 96 records in PubMed, 230 records in Embase and two trials were found by searching the reference lists. After review of titles and abstracts, 20 records were retrieved for evaluation and nine trials were eligible for inclusion[9,10,14-20] (Figure 1).

Five of the nine trials reported a positive effect of the diet on IBS symptoms superior to the control intervention[9,15,17,19,20] and four trials reported an equivalent symptomatic effect of the low FODMAP diet compared with the control intervention.

Of the nine RCTs, six trials used a parallel study design[10,14-16,18,19] and three used a crossover design[9,17,20] (Table 1).

The nine trials included a total of 542 patients (range: 15-123 patients; Table 1). Patients were primarily recruited in tertiary care and by advertisement (Table 1).

In three trials all meals were provided to the study participants.[9,17,20] The control meals reflected a typical Australian diet,[9] a typical American childhood diet[17] and a high FODMAP diet.[20] The FODMAP content in the typical Australian diet (24 g/d) exceeded the baseline FODMAP content (16 g/d)[9] and should therefore also be classified as a high FODMAP diet. The same applies to the typical American childhood diet (0.7 g/kg/d)[17] exceeding the FODMAP content of 12 g/d, as reported in the baseline diet of a comparable population in a study by the same authors.[21]

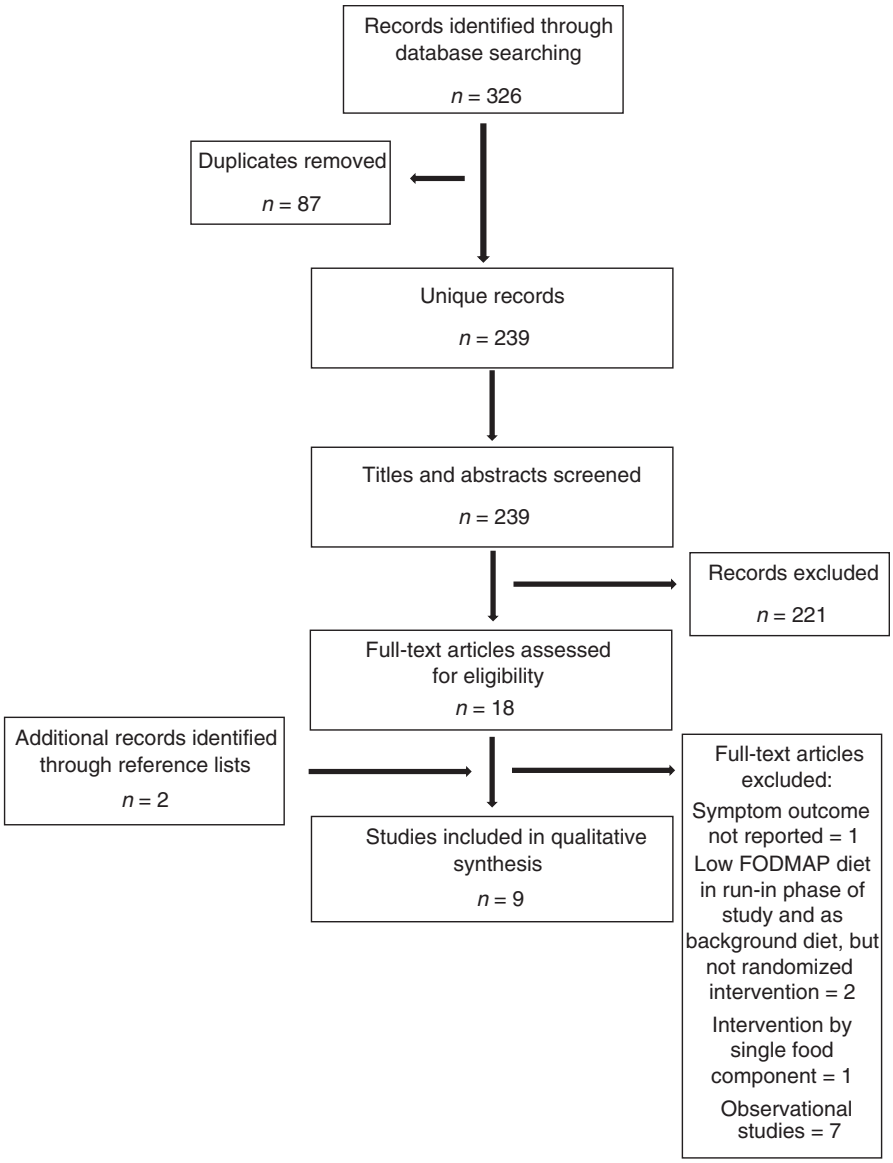

FIGURE 1 Flowchart of study selection

In six trials, the intervention consisted of instruction by a dietician in the low FODMAP diet.[10,14-16,18,19] No trials included the re-introduction phase in the intervention period, but in two trials participants were educated in reintroduction at the end of the intervention period.[10,18]

In the included trials, the intervention period was from 2 days to 6 weeks (Table 1) and one trial included a follow-up 6 months after the intervention.[10]

The critical review identified domains with a high risk of bias for all the trials (Table 2).

3.1 | Selection bias

Three trials had a low risk of bias in both domains assessing selection bias[15,18,19] (Table S1). Random sequence generation was performed in all nine trials and risk of bias was low in all except one trial with a skewed allocation.[14] Allocation concealment was described in three trials[15,18,19] and was unclear in six.[9,10,14,16,17,20]

3.2 | Performance bias

There was a high risk of performance bias in eight of the nine trials (Table S2). As the effect of the intervention relies primarily on subjective outcomes, the magnitude of performance bias is aggravated.

Participants were attempted blinded in six trials[14–17,20] (Table S2). Only one trial, which provided all meals to participants, evaluated the completeness of the blinding[9] and reported that 83% of the participants were able to identify the diet and were thus unblinded. Only one trial was double-blinded;[17] in the remaining eight trials the study personnel was not blinded.

TABLE 1 Randomised trials assessing symptomatic effects of a low FODMAP diet for IBS

Reference	Study design	Sample size	Setting	Intervention	Control	Duration	Follow-up	Definition of symptom improvement after intervention
Esweran[14]	Parallel	92	74% tertiary care 22% via advertisement 4% primary care	LFD (instructed by dietician)	Diet according to modified NICE guideline (instructed by dietician)	4 weeks	No follow-up	Primary endpoint: adequate relief 50% or more of the last 2 weeks of study period
Peters[10]	Parallel	74	Recruitment through advertisement in newspapers, on social media and on web-page	LFD (instructed by dietician)	Gut-directed hypnotherapy Combined control: LFD (instructed by dietician) and gut-directed hypnotherapy	6 weeks	6 months	>20 mm improvement on 100 mm VAS measuring GI symptoms
McIntosh[15]	Parallel	40	Tertiary care	LFD (instructed by dietician)	HFD (instructed by dietician)	3 weeks	No follow-up	Not defined. Symptoms measured by IBS-SSS
Böhn[16]	Parallel	75	Secondary and tertiary care One center also recruited through advertisement, but number of persons not stated	LFD (instructed by dietician)	Diet according to NICE guideline (instructed by dietician)	4 weeks	No follow-up	Responder defined as: ≥50 points reduction on IBS-SSS
Chumpitazi[17]	Crossover with wash-out period	52	Tertiary care (pediatric)	LFD (all meals provided)	TACD (all meals provided)	2 days on each diet	No follow-up	Responder defined as: ≥50% reduction in number of daily abdominal pain episodes during LFD and not during TACD
Pedersen[18]	Parallel	123	Tertiary care	LFD (instructed by dietician) All groups used web-application with an e-learning program on IBS, allowing patients to follow symptom development based on web registration	1. Probiotic LGG 2. Instructed to continue habitual diet	6 weeks	No follow-up	Improvement defined as: ≥50 points reduction on IBS-SSS
Halmos[9]	Crossover with wash-out period	30	Recruited through advertisement in breath test centers and community newspapers	LFD (all meals provided)	Standard Australian diet (all meals provided)	3 weeks on each diet	No follow-up	≥10 mm difference on 100 mm VAS scale considered clinically significant.
Staudacher[19]	Parallel	41	Tertiary care	LFD (instructed by dietician)	Instructed to continue habitual diet	4 weeks	No follow-up	Not defined. Symptoms measured daily by 4-point scale based on the GSRS and weekly by adequate symptom control.

(Continues)

TABLE 1 (Continued)

Reference	Study design	Sample size	Setting	Intervention	Control	Duration	Follow-up	Definition of symptom improvement after intervention
Ong[20]	Crossover with wash-out period	15	Tertiary care	LFD (all meals provided)	HFD (all meals provided)	2 days on each diet	No follow-up	Not defined. Symptoms measured on 3 point Likert scale. Composite score calculated for abdominal pain, bloating and wind

GI, gastro intestinal; GSRS, Gastrointestinal Symptom Rating Scale; HFD, high-FODMAP diet; LGG, Lactobacillus rhamnosus GG; NICE, National Institute for Clinical Health and Clinical Excellence; IBS, irritable bowel syndrome; IBS-SSS, IBS Symptom Severity Scale; LFD, low-FODMAP diet; TACD, traditional American childhood diet; VAS, visual analogue scale.

TABLE 2 For each domain risk of bias is rated as high, unclear or low

	Random sequence generation [a](Selection bias)	Allocation concealment [a](Selection bias)	Blinding of participants and personnel [b](Performance bias)	Blinding of outcome assesment [b](Detection bias)	Incomplete outcome data[c](Attrition bias)	Selective reporting [c](Reporting bias)	Choice of control group [d](Bias in design)	Objective evaluation of data[d](Interpretive bias)
Esweran[14]	Unclear risk	Unclear risk	High risk	Low risk	High risk	Low risk	High risk	High risk
Peters[10]	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk	High risk	Low risk
McIntosh[15]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	High risk	Low risk
Böhn[16]	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk	High risk	High risk
Chumpitazi[17]	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk
Pedersen[18]	Low risk	Low risk	High risk	High risk	High risk	High risk	High risk	Low risk
Halmos[9]	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk	High risk	High risk
Staudacher[19]	Low risk	Low risk	High risk	High risk	Low risk	High risk	High risk	High risk
Ong[20]	Low risk	Unclear risk	High risk	High risk	High risk	High risk	High risk	High risk

[a]Support for judgement in Table S1
[b]Support for judgement in Table S2
[c]Support for judgement in Table S3
[d]Support for judgement in Table S4

3.3 | Detection bias

Two trials[14,17] blinded the outcome assessment (Table S2). Only one trial, using instruction in the low FODMAP diet by a dietician,[14] reported blinded outcome assessment, even though this is recommended in trials challenged by difficulty with blinding.[22]

3.4 | Attrition bias

Three trials had a high risk for attrition bias[14,18,20] (Table S3). In two of the trials, incomplete outcome data was related to difficulty with the diet.[14,18] Persons, who withdrew from the study because they found the diet difficult or too restrictive, were excluded from the analyses, which might skew the outcome in favour of the low FODMAP diet.

3.5 | Reporting bias

Endpoint should be defined prior to conduction of the trial and the definition should be clear and clinically meaningful.[22] Three trials did not define endpoints in the methods section[18-20] (Table S3). Two of the trials[19,20] did not report changes in symptoms compared to baseline, as recommended,[22] but only compared symptoms between interventions. Six of the trials had low risk of reporting bias.

3.6 | Bias in design

A control group should consist of a placebo group or a group receiving a proven effective treatment creating a similar expectation of benefit.[22] All the included trials had a high risk of bias in the design due to choice of control group (Table S4). In the three trials providing all meals to participants,[9,17,20] the content of FODMAPs in the control diet exceeded the content of FODMAPs reported in baseline diets of IBS patients.[9,16,21,23]

In the six trials, which evaluated consultation on the low FODMAP diet by a dietician, a variety of control groups were used, all with limited established efficacy.

3.7 | Interpretive bias

Three trials had low risk of interpretive bias[10,15,18] (Table S4). The remaining trials had high risk of interpretive bias based on: weighting secondary endpoints higher than primary endpoints in the discussion and conclusion paragraphs;[14] failure to discuss possible unblinding of participants and placebo response;[9,16] concluding efficacy of the diet based on unconvincing data;[17,19] failure to discuss the fact that gas production was not associated to induction of symptoms;[20] and, concluding efficacy of the low FODMAP diet based on a comparison with a high FODMAP diet.[9]

3.8 | Other biases

Crossover design is usually discouraged because of the inherent methodological problems, primarily because of the potential for carry-over effects. The effects of the first treatment must not persist during the time when the second treatment is given. In addition, the crossover design increases the risk of patient unblinding. Three trials used a crossover design.[9,17,20] In the study by Halmos et al.,[9] the carry-over effect was limited by the washout period lasting at least 21 days or until symptoms had returned to baseline level and no order effect was observed. In the remaining two crossover trials,[17,20] there was no analysis of a potential carry-over effect and the washout period was fixed at 5 and 7 days. Furthermore, both trials[17,20] were limited to 2 days of intervention with limited clinical relevance.

4 | DISCUSSION

This is the first systematic review focusing on the quality of the trials evaluating the symptomatic effects of the low FODMAP diet for IBS patients. We found that all trials had domains with high risk of bias and the lack of blinding and choice of control group were the domains dominated by high risk in studies.

The RCTs included small numbers of patients primarily recruited from tertiary care, which may compromise generalizability. The included patients from tertiary care and breath test centres constitute a selected population that might be especially motivated for dietary intervention. Furthermore, there is a lack of trials investigating the effects of the diet in IBS patients in primary care, with only one study recruiting a limited number (4%) of patients from primary care.[14]

The intervention period of the trials was of short duration with a maximum of 6 weeks. IBS is usually a chronic, sometimes life-long, condition with periods of remission and exacerbation. Therefore, treatment trial lengths of a few days or a few weeks are generally considered insufficient for long term treatments and a minimum length of 6 months has been recommended to establish long-term efficacy[22]—at least for drug trials.

When establishing the effects of a novel treatment, interpretation of data can be complicated by pitfalls in the design. Development in symptoms that are not attributable to the treatment itself, such as a placebo response, regression towards the mean, the natural course of the disorder and observer and patient expectations, can lead to overestimation of the treatment response if the trial is not designed properly. The control groups in the trials, which estimated the effects of consultation by a dietician, unfortunately do not allow the discrimination of a proper effect of the diet from effects induced by other factors. Two trials[14,16] could not confirm that the low FODMAP diet is superior to standard dietary advice for IBS patients. The control group (standard dietary advice) reflects clinical practice and will probably induce a similar expectation of benefit as a low FODMAP diet. Unfortunately, standard of care dietary advice is also based on limited evidence.[24] In the study by Eswaran et al.,[14] the control group was instructed to eat small, frequent meals, avoid trigger foods and excess coffee and alcohol. The control group failed to adhere to the instructions but still reported a significant improvement in adequate relief and of similar magnitude as in the low FODMAP group, suggesting that the effect in the control group was driven by other factors than the intervention itself.

The low FODMAP diet was not superior to gut-directed hypnotherapy,[10] a treatment claimed to have effect on IBS symptoms[25] based on unblinded trials.

In two unblinded trials[18,19] the control group was randomised to continue their usual diet. This might impact negatively on the patients' expectations to symptom improvement as reflected by symptom deterioration in the control group at follow-up in the trial by Staudacher et al.[19] In the trial by Pedersen et al.,[18] the other control group was allocated to treatment with a probiotic not previously tested in IBS patients, which does not reflect standard of care.

Choosing a control group for an RCT which tests the effects of a diet is challenging and even more so in IBS with limited treatment options of established efficacy. Future trials should establish the symptomatic effects of a dietary intervention in subgroups of IBS patients with a specific phenotype, eg, IBS-C and use as the control arm an active treatment with proven efficacy eg, linaclotide.[26] Ideally, a double-blind, double-dummy design should be used to account for differences in the administration of the intervention (drug vs dietary advice).

In double-blinded trials providing all meals, a control diet with a FODMAP content reflecting habitual intake in the diet might serve as a placebo control, under the assumption that it has no symptomatic effects but can generate expectancy comparable to the active diet. In the included trials the effects of the low FODMAP diet was compared to a diet high in FODMAPs.[9,17,20] This comparison is not clinically relevant, as the control arm does not serve as a placebo group nor reflects standard of care. The fact that FODMAPs in high doses can provoke GI symptoms was established in a double-blinded, randomised, placebo-controlled, provocation study,[27] where patients reported an induction of GI symptoms during provocation with test drinks containing high-dose fructose or fructan mixtures. However, a similar induction of symptoms was not found by intake of lower doses relevant for standard meals.

Studying the symptomatic effects of a diet poses substantial challenges regarding design and implementation, partly because it is difficult to blind the intervention.

In general, blinding of patients to the low FODMAP diet can be challenging, especially in future trials because many patients with IBS are familiar with the concept as it is has gained much attention and information about the diet is available in excess. The performance bias introduced in the trials by lack of blinding can severely affect the interpretation of results, because the effect of the intervention is measured as subjective symptom outcomes highly susceptible to performance bias. Only one study, a crossover trial, evaluated the blinding of participants[9] and found that 83% of the participants were able to identify their diet and were thus unblinded. A lower intake of FODMAPs at baseline predicted a response to the low FODMAP diet in the study by Böhn et al.[16] This could indicate that patients with some knowledge of the diet prior to the intervention had a better symptom response that could be promoted by unblinding. When the intervention is difficult to blind, as in the six trials relying on dietary instruction, it should be reported if patients were able to identify the intervention,[22] but this was not the case in any of the studies.

There is a high placebo response in treatment trials of IBS patients, regardless of the character of the intervention.[28] The placebo response ranges from 3% to 84% in published IBS treatment trials.[29] In a meta-analysis of 76 placebo-controlled drug trials in IBS, Ford et al. found placebo rates between 0% and 91%, with higher rates in trials that used physician-reported outcomes and had a shorter duration of therapy.[30] In general, placebo responders mainly appear to be moderated by expectations of how the symptom might change after treatment or expectations of how symptom repetition can be coped with.[31] Several of the trials present data, which indicates that the postulated effect of the low FODMAP diet is primarily placebo driven, even though this possibility is discussed only to a limited extend in the articles. First, time to symptomatic effect on the low FODMAP diet varies considerably. In two trials,[17,20] the duration of the intervention was only 2 days and both reported a symptomatic effect. In one of the trials[20] an effect was reported already after 1 day, both on GI symptoms and on unspecific symptoms such as fatigue. Two trials[9,14] found the effect to occur after 7 days, and another trial[16] after 2 weeks. Second, a symptomatic effect of the diet has been reported for all IBS subtypes. Such a generalised effect of a dietary intervention on all stool types, as well as stomach pain, bloating, well-being and fatigue contributes to the impression of the effect being mainly driven by a placebo response. In the study by Halmos et al.,[9] a subjective effect of the low FODMAP diet on stool consistency was reported, but an objective evaluation of stool volume and consistency was unable to confirm this. Third, an interesting study investigated the effects of provocation with gluten in IBS patients with presumed non-celiac gluten sensitivity.[23] During an unblinded run–in period on the low FODMAP diet patients reported symptom improvement, whereas a deterioration in symptom control was reported in all three provocation arms (high gluten, low gluten, placebo), despite of a continued low FODMAP diet. This pattern suggests that the improvement during the run-in period was placebo driven, raised by the expectation of symptom relief and that the worsening during all three provocation arms was nocebo driven because the patients were convinced that gluten was responsible for their symptoms.

An important part of the low FODMAP diet is the reintroduction period, which should ensure a balanced diet with sufficient fibre intake. None of the included trials investigated the reintroduction period. One study conducted a follow-up after 6 months on patients returning a follow-up questionnaire[10] and reported that all but two reintroduced high FODMAP foods to their diet and that symptom improvement was maintained. In general, there is a lack of data on what characterises the diet after reintroduction in terms of what foods are typically reintroduced or avoided in the long term, including fibre intake. A limited characterisation of reintroduced foods was described in a retrospective questionnaire study.[32] At 15 months follow-up, 84% of patients lived on a modified diet with some foods rich in FODMAPs and wheat; dairy products and onions were least often reintroduced.[32] Other studies have reported that dairy products, onions and wheat are avoided by IBS patients not educated in the low FODMAP diet[2,4] and it is not clear if the limited reintroduction of these food items reflects a general tendency in IBS patients.

The full concept of dietary instruction in the low FODMAP diet, including a reintroduction period as a treatment for IBS symptoms, has not yet been sufficiently studied limiting the applicability of study results to a clinical setting.

5 | CONCLUSIONS

The recommendation of the low FODMAP diet as a first-line treatment for patients with IBS is based on randomised interventional trials characterized by high risk of bias, primarily due to lack of proper blinding and choice of control group. Trials in unselected IBS patients in primary care are lacking. The low FODMAP diet has not been studied in a randomised, controlled setting for more than 6 weeks and trials examining the effect of the important reintroduction period are lacking. There are many indications in the published literature to suggest that the symptomatic effects of the low FODMAP diet are primarily driven by a placebo response.

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Author contributions: Laura Rindom Krogsgaard: Searched for trials, reviewed trials, interpreted data, drafted the manuscript. Malene Lyngesen: Contributed to the manuscript. Peter Bytzer: Reviewed trials, interpreted data, contributed to the manuscript.

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LINKED CONTENT

This article is linked to Quigley paper. To view this article visit https://doi.org/10.1111/apt.14140.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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