A Low-FODMAP Diet Improves the Global Symptoms and Bowel Habits of Adult IBS Patients: A Systematic Review and Meta-Analysis

Jinsheng Wang†, Pengcheng Yang†, Lei Zhang* and Xiaohua Hou*

Department of Gastroenterology, Tongji Medical College, Union Hospital, Huazhong University of Science and Technology, Wuhan, China

Background: A low-fermentable oligo-, di-, monosaccharides, and polyols (FODMAP) diet has been reported to be associated with improving the symptoms of irritable bowel syndrome (IBS); however, its efficacy as evaluated by different studies remains controversial.

Objective: A systematic review and meta-analysis of randomized controlled trials (RCTs) were conducted to explore the efficacy of a low-FODMAP diet (LFD) in alleviating the symptoms of IBS.

Methods: A search of the literature for RCTs that assessed the efficacy of an LFD in treating IBS patients was conducted using the electronic databases PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science. The searches in each database were conducted from the inception of the database to February 2021. Two independent reviewers screened citations and a third reviewer resolved disagreements. Two independent reviewers also performed eligibility assessments and data extraction. The RCTs that evaluated LFDs vs. a normal IBS or usual diet and assessed changes of IBS symptoms were included in the search. Data were synthesized as the relative risk of global symptoms improvement, mean difference of IBS Severity Scoring System (IBS-SSS) score, sub-items of IBS-SSS irritable bowel syndrome-related quality of life (IBS-QOL), hospital anxiety and depression scale (HADS), stool consistency/frequency, and body mass index (BMI) using a random effects model. The risk of bias was assessed using Risk of Bias Tool 2 (RoB 2). The bias of publication was assessed based on Egger’s regression analysis. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Results: A total of 2,768 citations were identified. After full-text screening, a total of 10 studies were eligible for the systematic review and were subsequently used to compare an LFD with various control interventions in 511 participants. An LFD was associated with the improvement of global symptoms \([n = 420; \text{Risk Ratio (RR)} = 1.54; 95\% \text{ Confidence Interval (CI) } 1.18 \text{ to } 2; I^2 = 38\%]\), improvement of stool consistency \([n = 434; \text{Mean difference (MD)} = -0.25; 95\% \text{ CI } -0.44 \text{ to } -0.06; I^2 = 19\%]\), and a reduction trend of stool frequency \([n = 434; \text{MD} = -0.28; 95\% \text{ CI } -0.57 \text{ to } 0.01; I^2 = 68\%]\) compared
INTRODUCTION

Irritable bowel syndrome is one of the most prevalent chronic gastrointestinal diseases, with a prevalence of ~7–21% (1, 2). In some Western countries, the prevalence of irritable bowel syndrome (IBS) is around twice as high in females than in males, which may be higher in Asian countries (1). The diagnosis of IBS is based on the association of recurrent abdominal pain with altered bowel habits, namely, diarrhea and/or constipation, in the absence of organic diseases, such as inflammatory bowel disease or colon cancer (2). IBS is usually categorized into subtypes according to predominant bowel habits: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M), or unsubtyped IBS (IBS-U) (1–3). Irritable bowel syndrome has been conceptualized as a brain–gut disorder (4), which is also associated with poor quality of life, impaired social function (5), and psychological-psychiatric conditions, such as anxiety and depression (6–8). Medications that improve diarrhea (e.g., loperamide, probiotics) or constipation (e.g., fiber supplements, laxatives) are used as the first-line IBS therapies to improve altered bowel habits but offer little benefit for abdominal pain, bloating, and psychosocial problems (1, 2). Up to 70% of IBS patients report that symptom onset or exacerbation are associated with certain food, such as milk and milk products, wheat products, caffeine, cabbage, onion, peas, beans, hot spices, and fried and smoked food (3, 9–11). Some IBS patients tend to avoid certain food items and try gluten-free or lactate-free diets to prevent the onset of their symptoms (12, 13). However, these avoidances of food may make them susceptible to long-term nutritional deficiencies and low body weight (14).

Restricting food with highly fermentable oligo-, di-, monosaccharides, and polyols (FODMAPs), which can trigger and/or exacerbate IBS symptoms, may contribute to managing IBS symptoms according to a growing body of clinical trials (15–19). Examples of FODMAPs include fructose, lactose, sugar alcohols (sorbitol, maltitol, mannitol, xylitol, and isomalt), fructans, and galactans, which are widely presented in a large range of food, such as wheat, rye, vegetables, fruits, and legumes (20).

with control interventions. There was no statistically significant change in IBS-QOL \( (n = 484; \text{MD} = 2.77; 95\% \text{ CI} -2 \text{ to } 7.55; I^2 = 62\% ) \), anxiety score \( (n = 150; \text{MD} = -0.45; 95\% \text{ CI} -3.38 \text{ to } 2.49; I^2 = 86\% ) \), depression score \( (n = 150; \text{MD} = -0.05; 95\% \text{ CI} -2.5 \text{ to } 2.4; I^2 = 88\% ) \), and BMI \( (n = 110; \text{MD} = -0.22; 95\% \text{ CI} -1.89 \text{ to } 1.45; I^2 = 14\% ) \). The overall quality of the data was “moderate” for “global improvement of IBS symptom,” “stool consistency,” “stool consistency for IBS with diarrhea (IBS-D),” and “stool frequency for IBS-D,” and “low” or “very low” for other outcomes according to GRADE criteria.

Conclusion: An LFD is effective in reducing the global symptoms and improving the bowel habits of adult IBS patients. The efficacy for IBS-D patients can also be more pronounced.

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Keywords: FODMAP, diet, irritable bowel syndrome, quality of life, meta-analysis, HADS
Study Selection
The inclusion criteria were presented as the following: (1) randomized controlled trials (including cross-over trials); (2) participants aged ≥ 18 years; (3) an objective basis for diagnosis (Rome I, II, III, or IV); (4) comparing LFD with a placebo diet or a usual diet; (5) outcomes including global improvement in IBS symptoms, IBS-QOL, HADS, stool consistency/frequency, or BMI; (6) the duration of therapy ≥ 3 weeks. The exclusion criteria were presented as the following: (1) non-randomized controlled trials, cohort studies, retrospective studies, or case reports, (2) participants aged < 18 years, (3) participants suffered from other digestive disorders, such as inflammatory bowel disease, (4) participants in the experimental group received multiple interventions at the same time. Two independent reviewers (Wang JS and Yang PC) performed the data abstraction for this study. Data extracted included data on different reasons, leaving a total of 10 studies that were eligible for the systematic review, comparing an LFD with control diets (including the traditional IBS diet, high-FODMAP diet, or usual diet) in 511 participants (Figure 1). A summary of the trial characteristics is given in Table 1.

Outcome Assessment
The primary outcome was assessed according to the global improvement in IBS symptoms. Secondary outcomes included IBS-QOL, stool consistency/frequency, HADS, and BMI.

Data Extraction
Two independent reviewers (WJ and YP) performed the data abstraction for this study. Data extracted included data on the year of publication, country of origin, design of the study, clinically meaningful improvement standard, duration of therapy, IBS criteria, IBS subtype involved, the comparator intervention, and outcomes. Risk ratio of symptom improvement was abstracted as an intention-to-treat analysis, and the dropouts would be treated in the groups to which they had been initially randomized. The mean difference of the IBS Severity Scoring System (IBS-SSS) score, sub-items of IBS-SSS (including “pain intensity,” “pain frequency,” “abdominal distension,” “dissatisfaction of bowel habit,” and “interference on life in general”), IBS-QOL score, HADS score, stool consistency and frequency score, and BMI were assessed. Disagreements were resolved by a third reviewer (ZL).

Assessment of Risk of Bias and GRADE Methodology
The risk of bias assessment was performed by two independent reviewers (WJ and YP) using the Cochrane Risk of Bias Tool with Review Manager (RevMan) (Version 5.3, Cochrane Collaboration). Each study was evaluated based on the reporting of randomization, allocation, blinding, and outcome assessment and reporting. Data was analyzed to assess the quality of evidence according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology using the GRADEPro Guideline Development Tool (GDT) (33).

RESULTS

Search Results and Study Selection
The literature search identified 2,768 citations through electrical databases, and 46 studies underwent full manuscript review. After full-text screening, 36 articles were excluded for different reasons, leaving a total of 10 studies that were eligible for the systematic review, comparing an LFD with control diets (including the traditional IBS diet, high-FODMAP diet, or usual diet) in 511 participants (Figure 1). A summary of the trial characteristics is given in Table 1.

Global Improvement of Symptoms
Seven studies reported the global improvement of symptoms with different clinically meaningful improvement definitions as dichotomous outcomes (Figure 2), where an LFD was associated with an improvement of global symptoms in IBS patients compared with controls (n = 420; RR = 1.54; 95% CI 1.18–2; I² = 38%). Five studies assessed global symptom changes using IBS-SSS as continuous variables, showing that an LFD was associated with a reduction in total IBS-SSS score (n = 354; MD = −37.72; 95% CI −53.97 to −21.46; I² = 40%) (Figure 3), pain intensity (n = 354; MD = −11.27; 95% CI −16.32 to −6.23; I² = 47%) (Supplementary Figure 1), pain frequency (n = 354; MD = −9.11; 95% CI −16.26 to −1.96; I² = 73%) (Supplementary Figure 2), interference on life in general (n = 354; MD = −11.58; 95% CI −13.92 to −9.24; I² = 0%) (Supplementary Figure 3), and dissatisfaction of bowel habit (n = 354; MD = −8.95; 95% CI −12.6 to −5.31; I² = 26%) (Supplementary Figure 4), but with no statistically significant effect on abdominal distension (n = 354; MD = −4.82; 95% CI −10.75 to 1.11; I² = 57%) (Supplementary Figure 5).

Stool Output
Six studies reported the improvement of stool output in IBS patients due to an LFD. An LFD also showed significant effects on stool consistency scores (n = 434; MD = −0.25; 95% CI −0.44 to −0.06; I² = 19%) (Figure 4), and a trend of reduced stool frequency per day (n = 434; MD = −0.28; 95% CI −0.57 to 0.01; I² = 68%) (Figure 5) compared with control interventions. Interestingly, the improvement of stool output in IBS-D patients seemed to be more sensitive to an LFD according to subgroup
FIGURE 1 | Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the included studies. RCT, randomized controlled trial.

analysis: stool consistency score ($n = 183; \text{MD} = -0.34; 95\% \text{ CI} = -0.55 \text{ to } -0.14; I^2 = 0\%$) (Figure 4) and stool frequency ($n = 183; \text{MD} = -0.67; 95\% \text{ CI} = -0.96 \text{ to } -0.38; I^2 = 0\%$) (Figure 5).

IBS-QOL
The irritable bowel syndrome-related quality of life score was analyzed using the synthesis from five studies, showing no significant changes ($n = 484; \text{MD} = 2.77; 95\% \text{ CI} = -2 \text{ to } 7.55; I^2 = 62\%$). Subgroup analysis based on IBS subtype showed no statistical difference between subgroups ($p = 0.48$) (Figure 6).

HADS
Two studies reported HADS, however, both showed no difference between low-FODMAP groups and controls: anxiety score ($n = 150; \text{MD} = -0.45; 95\% \text{ CI} = -3.38 \text{ to } 2.49; I^2 = 86\%$) (Figure 7) and depression score ($n = 150; \text{MD} = -0.05; 95\% \text{ CI} = -2.5 \text{ to } 2.4; I^2 = 88\%$) (Figure 8).
TABLE 1 | Baseline characteristics of the studies included in the meta-analysis.

| References | Design | Duration | IBS definition | IBS type | Age range or mean age (SD)/year | Female/total | Intervention | Participants (LFD/ND) | Drops (LFD/ND) | Clinically meaningful improvement | Symptom assessment |
|------------|--------|----------|----------------|----------|--------------------------------|--------------|-------------|----------------------|---------------|----------------------------------|------------------|
| Böhn et al. (22) Sweden | Multi-center parallel single-blind RCT | 4 weeks | ROME III | IBS-D, IBS-C, IBS-M, IBS-U | 43 (16) | 56/67 | Traditional IBS diet vs. LFD | 33/34 | 5/3 | A reduction in IBS-SSS ≥ 50 | IBS-SSS, Stool consistency/frequency, BMI, HADS |
| Halmos et al. (21) Australia | Single-blind cross-over RCT | 3 weeks | ROME III | IBS-D, IBS-C, IBS-M, IBS-U | 23–60 | 21/30 | Typical Australian diet vs. LFD | 30/24 | 5/2 | A reduction in VAS ≥ 10 mm | IBS-SSS |
| McIntosh et al. (18) Canada | Single-blind parallel RCT | 3 weeks | ROME III | IBS-D, IBS-C, IBS-M, IBS-U | 18–62 | 32/37 | High FODMAP diet vs. LFD | 18/19 | 5/2 | A reduction in IBS-SSS ≥ 50 | IBS-SSS |
| Staudacher et al. (24) the UK | RCT | 4 weeks | ROME III | IBS patients with bloating and/or diarrhea as major IBS symptom | LFD:35.2 (11.4) ND:35.0 (8.7) | 23/35 | Habitual diet vs. LFD | 19/16 | 1/2 | Answer “yes” to “Were your symptoms adequately controlled over the previous week?” | Global symptom question; Stool consistency/frequency |
| Staudacher et al. (25) the UK | Multi-center 2 × 2 factorial RCT | 4 weeks | ROME III | IBS-D, IBS-M, IBS-U | LFD:36 (11) ND:33 (12) | 70/104 | Sham diet vs. LFD | 51/53 | 2/1 | Answer “yes” to “Did you have adequate relief of your symptoms over the past 7 days?” | “Adequate symptom relief” question; IBS-SSS, IBS-QOL, Stool consistency/frequency |
| Wilson et al. (26) the UK | Double-blind 3-arm RCT | 4 weeks | ROME III | IBS-D, IBS-C, IBS-M, IBS-U | LFD:38.9 (10.0) ND:30.3 (9.8) | 25/45 | Sham diet vs. LFD | 21/21 | 4/3 | Answer “yes” to “Over the past 7 days, do you feel that you have had adequate relief of your IBS symptoms?” | “Adequate symptom relief” question; IBS-SSS, IBS-QOL, Stool consistency/frequency |
| Zahedi et al. (19) Iran | Single-blind RCT | 6 weeks | ROME III | IBS-D | LFD:37.60 (11.9) ND:37.43 (13.27) | 51/101 | GDA vs. LFD | 50/51 | 2/3 | – | IBS-SSS, IBS-QOL, Stool consistency/frequency, HADS |

(Continued)
| References          | Design                  | Duration | IBS definition | IBS type | Age range or mean age (SD)/year | Female/total | Intervention | Participants (LFD/ND) | Drops (LFD/ND) | Clinically meaningful improvement | Symptom assessment |
|---------------------|-------------------------|----------|----------------|----------|--------------------------------|--------------|--------------|----------------------|----------------|-------------------------------|---------------------|
| Eswaran et al. (23) | Single-center single-blind RCT | 4 weeks  | ROME III       | IBS-D    | LFD: 41.6 (14.7) ND: 43.8 (15.2) | 65/92        | mNICE vs. LFD | 45/39                | 8/9            | –                            | IBS-QOL; HADS       |
| Eswaran et al. (15) | Single-center single-blind RCT | 4 weeks  | ROME III       | IBS-D    | LFD: 41.6 (14.7) ND: 43.8 (15.2) | 65/92        | mNICE vs. LFD | 45/39                | 8/9            | Answer “yes” to “In regard to all your IBS symptoms, as compared with the way you felt before you started the diet, have you, in the past seven days, had adequate relief of your IBS symptoms?” | “Adequate symptom relief” question; Stool consistency/frequency |
| Laatikainen et al. (17) | Double-blind cross-over RCT | 4 weeks  | ROME III       | IBS-D    | 42.9 (21–64)                 | 73/80        | Regular rye bread vs. Low-FODMAP rye bread | 80/80                | 4/6            | –                            | IBS-SSS; IBS-QOL     |

RCT, randomized controlled trial; BMI, body mass index; FODMAP, fermentable oligo-di-mono-saccharides and polyols; LFD, low fermentable oligo-di-mono-saccharides and polyols diet; GDA, general dietary advice; IBS-D, irritable bowel syndrome with diarrhea; IBS-M, mixed stool pattern irritable bowel syndrome; IBS-C, constipation predominant irritable bowel syndrome; IBS-U, unclassified irritable bowel syndrome; VAS, visual analog scale; HADS, hospital anxiety and depression scale; IBS-SSS, irritable bowel syndrome-severity symptom scale; IBS-QOL, irritable bowel syndrome related quality of life; mNICE, modified diet recommended by the National Institute for Health and Care Excellence; vs., versus.
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FIGURE 2 | Pooled relative risk for the improvement of irritable bowel syndrome (IBS) global symptoms. LFD, low-FODMAP diet; ND, normal diet.

TABLE 1 | Relative Risk of Improvement of IBS Global Symptoms

| Study or Subgroup | LFD | ND | M-H, Random, 95% CI |
|-------------------|-----|----|---------------------|
| Eswaran 2016      | 24  | 16 | 1.27 [0.80, 2.03]   |
| Subtotal (95% CI) | 46  | 39 | 1.27 [0.80, 2.03]   |

Total events: 16
Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)

1.6.2 including all subtypes

Böhn 2015
Halmos 2014
Mcintosh 2017
Staudacher 2012
Staudacher 2017
Wilson 2020
Subtotal (95% CI)

Total events: 103
Heterogeneity: Tau² = 0.07; Chi² = 9.14, df = 5 (P = 0.10); I² = 45%
Test for overall effect: Z = 2.99 (P = 0.003)

Total (95% CI): 209
Heterogeneity: Tau² = 0.04; Chi² = 9.60, df = 6 (P = 0.14); I² = 38%
Test for overall effect: Z = 3.20 (P = 0.001)
Test for subgroups: Chi² = 0.71, df = 1 (P = 0.40), I² = 0%

FIGURE 3 | Pooled mean difference for the improvement of IBS global symptoms. LFD, low-FODMAP diet; ND, normal diet.

TABLE 2 | Mean Difference

| Study or Subgroup | LFD | ND | Mean Difference |
|-------------------|-----|----|------------------|
| Böhn 2015         | 246 | 127| 10.00 [40.65, 60.65] |
| McIntosh 2017     | 208 | 74.8| -82.00 [-140.87, -23.13] |
| Staudacher 2017   | 173 | 95 | -51.00 [-86.41, -15.59] |
| Wilson 2020       | 183 | 19.1| -33.30 [-44.29, -22.31] |
| Zahedi 2018       | 108 | 63.8| 41.75 [-64.37, -9.13] |

Total (95% CI): 174
Heterogeneity: Tau² = 127.87; Chi² = 6.68, df = 4 (P = 0.15); I² = 40%
Test for overall effect: Z = 4.55 (P < 0.00001)

BMI

Only two studies reported the effect of LFD on BMI changes, but showed no statistical difference (n = 110; MD = −0.22; 95% CI −1.89 to 1.45; I² = 14%) (Figure 9).

Risk of Bias and GRADE

The overall risk of bias is relatively low as shown in Figure 10. A summary of the quality of evidence according to GRADE for the included RCTs is given in Table 2.

Publication Bias

There was no evidence of publication bias based on Egger's regression analysis: global improvement of symptoms (p = 0.0765); IBS-SSS (p = 0.1558); pain intensity (p = 0.7638); pain frequency (p = 0.7686); abdominal distension (p = 0.7689); dissatisfaction of bowel habit (p = 0.1871); interference on life in general (p = 0.0785); IBS-QOL (p = 0.1086); stool consistency (p = 0.4353); stool frequency (p = 0.9699).

Subgroup Analysis

Subgroup analysis of the outcomes (except “HADS” and “BMI” because only 2 RCTs were included for each outcome) was conducted based on “treatment duration,” “FODMAP level in the control diet,” “definition of clinically meaningful improvement,” and “IBS subtype.” Results are shown in Supplementary Table 1.

DISCUSSION

This updating meta-analysis included 10 high-quality RCT studies involving 511 participants according to the above criteria. The study aimed to provide clinicians with evidence-based data proving that an LFD alleviates symptoms in patients with IBS.
More research data were attempted to be extracted from existing studies to explore the effects of an LFD on the overall symptoms, stool output, IBS-QOL, anxiety and depression, and BMI of IBS patients. The study found that an LFD significantly reduced the global symptoms of patients with IBS and improved their stool output, especially for those with IBS-D, and that the quality of evidence was moderate. However, LFDs had no statistically significant effects on IBS-QOL, anxiety and depression score, and BMI in patients with IBS, while the quality of evidence was low or very low. The reasons for the low level of evidence quality mainly include inappropriate blinding methods, large heterogeneity, and a limited number of studies. Even though some potential limitations and concerns of an LFD have been raised, such as nutritional adequacy, cost, difficulty in teaching, learning, and continuing, most of the limitations (20, 34). In conclusion, based on the evidence presented in this meta-analysis, adult IBS patients, especially those with IBS-D, are recommended to try an LFD with professional advice from healthcare professionals.

Global symptom improvement was treated as the primary outcome in this systematic review. Seven studies (15, 18, 21, 22, 24–26) evaluated the effectiveness of an LFD in improving
FIGURE 6 | Pooled mean difference for irritable bowel syndrome-related quality of life (IBS-QOL). LFD, low-FODMAP diet; ND, normal diet.

FIGURE 7 | Pooled mean difference for anxiety score based on the hospital anxiety and depression scale. LFD, low-FODMAP diet; ND, normal diet.

FIGURE 8 | Pooled mean difference for depression score based on the hospital anxiety and depression scale. LFD, low-FODMAP diet; ND, normal diet.

FIGURE 9 | Pooled mean difference for body mass index (BMI). LFD, low-FODMAP diet; ND, normal diet.
the overall symptoms of IBS with dichotomous variables, using different clinically meaningful improvement criteria. Meanwhile, there were 5 RCTs (18, 19, 22, 25, 26) that used IBS-SSS to assess the IBS global symptoms with continuous variables, which also supported this conclusion. According to the results, over 60% (127/209) of IBS patients in the LFD group experienced significant relief, which seems to be an acceptable result; whereas, GRADE (35) would ideally require 300 responders to be classified as robust. More large-sample studies are needed to provide reliable evidence in the future. However, it is a challenge to conduct a high-quality RCT on this subject due to a lack of support from the pharmaceutical industry and funding agencies (27). Three previous meta-analyses used “mean difference” or “standardized mean difference” based on IBS-SSS as their effect sizes (30, 31, 36). These two kinds of effect sizes can only reflect the effect of an LFD on the IBS population, but cannot evaluate individual differences. At the same time, a statistically significant mean difference may not be clinically significant. For example, a 50-point reduction in IBS-SSS is generally considered to reflect a clinically meaningful improvement (22, 37). Thus, risk ratio (RR) was chosen to evaluate the difference between LFD and control diets, trying to make the results more clinically meaningful and easier to understand. In addition, comparing responder rates between trials is difficult because of the different responder definitions that were used (22). A 50-point reduction of IBS-SSS in two trials (18, 22) and a 10-point reduction in the visual analog scale (VAS) in one trial (21) were considered to reflect a clinically meaningful improvement. On the other hand, patients who felt adequate relief of their IBS symptoms were seen as responders in another four papers (15, 24–26). The existing scales for assessing the severity of IBS symptoms are not uniform, and it makes no sense to directly pool these scores together for meta-analysis. If the continuous variables of scores from a scale can be transformed into a dichotomous variable according to an appropriate “responding criteria,” the results of these clinical trials can be directly compared despite the different scales. Moreover, dropout is inevitable in clinical research and the reasons should be clarified. For instance, in patients who were intolerant of the intervention: the data of these results should be attributed to treatment failure rather than simple data loss in an intention-to-treat analysis.

According to ROME III (2, 38) and IV (4, 39) criteria, IBS is diagnosed on the basis of recurrent abdominal pain related to defecation or in association with a change in stool frequency or form. Thus, the effect of LFDs on altered bowel habits in IBS patients is an important aspect to evaluate. To our knowledge, this is the first meta-analysis that included stool output as a crucial outcome on this subject, which has not been demonstrated by previous meta-analyses (27–31). Stool consistency generally refers to the rheology or viscosity of the stool, which is largely determined by stool water content (40, 41). Gastrointestinal water absorption is limited by rapid intestinal transit limits, causing loose or liquid stools (42). It can be measured as a finite number of categories by the Bristol Stool Form Scale (BSFS), which is the most widely used criteria (43, 44). According to our study, pooled data from six RCTs showed a moderate improvement in the stool output of IBS patients following an LFD, which was consistent with a previous meta-analysis study (only containing three RCTs for this outcome) (28). Interestingly, patients with IBS-D (however, only 93 IBS-D patients were included) seemed to benefit more from an LFD, probably obtaining a greater improvement in stool output than other IBS subtypes according to the subgroup analysis. The results mentioned above indicate that an LFD may contribute to reduced stool water content, increase stool hardness, and further reduce stool frequency effectively. Nevertheless, according to this theory, constipation in IBS-C patients would not be improved by an LFD and may even be worsened. However, more research is needed in the future to confirm this.

Irritable bowel syndrome affects the quality of life negatively (44–46), to the same degree as organic gastrointestinal disorders
### TABLE 2 | Grading of recommended assessment, development and evaluation (GRADE) summary of findings.

| Participants (studies) follow up | Risk of bias | Inconsistency | Indirectness | Imprecision | Publication bias | Overall certainty of evidence | Study event rates (%) | Relative effect (95% CI) | Anticipated absolute effects |
|---------------------------------|--------------|---------------|--------------|-------------|-----------------|-------------------------------|------------------------|--------------------------|-----------------------------|
| **Global improvement of IBS symptom** | (7 RCTs) | Serious | Not serious | Not serious | None | □□□□ MODERATE | 82/211 (38.9%) | 127/209 (60.8%) | RR 1.58 (1.29–1.93) | 389 per 1,000 (from 113 more to 361 more) |
| **Stool consistency** | (6 RCTs) | Serious | Not serious | Not serious | None | □□□□ MODERATE | 219 | 215 | – | The mean stool consistency was 4.41 |
| **Stool frequency** | (6 RCTs) | Serious | Not serious | Not serious | Serious | □□□□ □□ □□ □□ MODERATE | 219 | 215 | – | The mean stool frequency was 2.24 |
| **Stool consistency for IBS-D** | (2 RCTs) | Not serious | Not serious | Not serious | Serious | □□□□ □□ □□ □□ □□ MODERATE | 90 | 93 | – | The mean stool consistency for IBS-D was 4.74 |
| **Stool frequency for IBS-D** | (2 RCTs) | Not serious | Not serious | Not serious | Serious | □□□□ □□ □□ □□ □□ MODERATE | 90 | 93 | – | The mean stool frequency for IBS-D was 2.88 |
| **IBS related quality of life** | (6 RCTs) | Serious | Not serious | Serious | None | □□□□ □□ □□ □□ □□ MODERATE | 279 | 276 | – | The mean IBS related quality of life was 51.59 |
| **Anxiety score** | (2 RCTs) | Serious | Not serious | Serious | None | □□□□ □□ □□ □□ □□ MODERATE | 74 | 76 | – | The mean anxiety score was 8.30 |
| **Depression score** | (2 RCTs) | Serious | Very serious | Not serious | Serious | □□□□ □□ □□ □□ □□ MODERATE | 74 | 76 | – | The mean depression score was 4.32 |
| **BMI** | (2 RCTs) | Serious | Not serious | Not serious | None | □□□□ □□ □□ □□ □□ MODERATE | 56 | 54 | – | The mean BMI was 24.78 |

CI, Confidence interval; RR, Risk ratio; MD, Mean difference.
like Crohn’s disease (47). This imposes a substantial burden on patients and employers (45, 46), which suggests a significant unmet need for effective therapies to treat the symptoms of IBS and alleviate the considerable societal and patient burden associated with this condition. The IBS-QOL, validated in 1998 by Patrick et al. (48) is utilized as a conceptually valid self-administered questionnaire with highly reproducible results for assessing the perceived quality of life for individuals with IBS (48). Meaningful clinical improvement is seen by a rise in IBS-QOL score > 14 (48). Six RCTs involved the evaluation of the effects of an LFD on this term with relatively high heterogeneity. Sensitivity analysis showed that the greatest heterogeneity among the studies came from Eswaran et al. (23). When this study was excluded, the heterogeneity index I^2 decreased from 62 to 0%. However, the final result was still not statistically significant, suggesting that no clinical improvement in this term occurred after an LFD intervention in IBS patients. Consistent results were observed in the subgroup analysis based on IBS subtype. It is important to note that restrictive diets can sometimes be stressful for patients with chronic diseases. Any effort to eliminate more food or impose further dietary restrictions might hamper the adherence rate, produce opposite results, and have a negative effect on the quality of life in patients with IBS (49). In the LFD group, in particular, available dietary choices were restricted to a great degree, reducing long-term adherence (20, 33). Ooi et al. (50) and Halmos (51) noted that extensive or inappropriate use of the LFD could have a negative impact on the health of patients. On the other hand, the duration of most LFD trials was limited (<8 weeks) and could not ensure long-term efficacy comparable to the drug trials (52). An additional period may be necessary for clinically significant improvement in quality of life for IBS patients to manifest following an LFD.

Major psychosocial problems have been reported to be observed in 50–60% of IBS patients (6). Three pieces of meta-analyses showed that levels of anxiety and depression were significantly higher in IBS patients compared with healthy controls (6–8). Meanwhile, the prevalence rates of anxiety and depression symptoms in IBS patients are near 40 and 30%, respectively (6). It is not difficult to accept that chronic IBS symptoms can have a destabilizing impact on quality of life and be associated with stress, work impairment, and further aggravation of mental disorders. However, there was no significant difference in the anxiety and depression scores between LFD and control groups in the included studies. Eswaran et al. (23) demonstrated that LFDs could alleviate the symptoms of anxiety but not have any effects on depression. The other study conducted by Bohn et al. (22) showed that LFDs had no effect on depression in patients with IBS. At present, a limited number (only two papers included in this study) of studies cannot come to a definite conclusion on this proposition, and further studies are needed to put more focus on the effect of LFDs on improving the anxiety and depression statuses of IBS patients.

Quality assessment of the RCTs yielded high risk in the blinding process of one RCT (24) and in the outcome assessment process of another two RCTs (15, 23), although the overall risk of bias was relatively low. We used the GRADE methodology (53) to evaluate the quality of the evidence, which is the most widely accepted approach. Eventually, it was found that the evidence supporting the significant effects of LFDs on IBS symptoms was relatively reliable. Generally, the blinding of patients to the LFD can be challenging (52). Many IBS patients are aware of the concept of an LFD, and information on this diet is freely available. An IBS patient can easily deduce which diet they have been allocated to if they participate in an RCT. Only one paper (21) that was included had assessed blinding to the diets by asking participants to identify the diet that they had been allocated to prove the success of the blinding process. Therefore, adhering to a diet regime that is considered “healthy” might reduce anxiety and subsequently alleviate IBS symptoms; thus creating a placebo response. Most studies [except the three studies (15, 19, 23) that had only recruited IBS-D patients] did not address differences in responses to dietary interventions in IBS subgroups, making it difficult to demonstrate a difference in the response rates and other outcomes among IBS subtypes. However, according to the subgroup analysis, IBS-D patients seemed to get more benefits from an LFD in improving their bowel habits.

As reported, FODMAPs have important physiological effects: they increase stool bulk, enhance calcium absorption, modulate immune function, and decrease the levels of serum cholesterol, triacylglycerols, and phospholipids (48). Because of the effects mentioned above, many potential limitations and concerns about LFDs have been raised (21, 51) such as nutritional adequacy, cost, and difficulty in teaching, learning, and continuing the diet. Although a relatively short-term (<6 weeks) LFD was generally well-tolerated, with adverse events rarely reported (16, 26), the pooled mean difference of BMI was not statistically significant between LFD and control groups according to our study. The effects, both positive and negative, of a long-term LFD on IBS still need to be assessed by expanding the sample quantity and extending the time of intervention (52). Therefore, a minimum length of 6 months has been recommended to establish long-term efficacy (53).
patients and lead to a certain degree of heterogeneity among different studies.

In conclusion, this systematic review and meta-analysis provide a moderate quality of evidence for supporting the efficacy of an LFD in the improvement of global symptoms and bowel habits of adult IBS patients. The improvement in bowel habits seems to be more pronounced in IBS-D patients. Recommending adult IBS patients, especially those with IBS-D, to try an LFD with professional advice from health care professionals is worth promoting.

**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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**AUTHOR CONTRIBUTIONS**

JW came up with the idea of the study. JW and LZ designed the research. JW, PY, LZ, and XH conducted the research, analyzed the data, and performed the statistical analysis. JW and PY wrote initial version. LZ and XH provided critical input. All authors had equal responsibility for the final content of the paper, read, and agreed to the published version of the manuscript.

**SUPPLEMENTARY MATERIAL**

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