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Meta-analyses

The efficacy and real-world effectiveness of a diet low in fermentable oligo-, di-, monosaccharides and polyols in irritable bowel syndrome: A systematic review and meta-analysis

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SUMMARY

Background & aims: A diet low in fermentable oligo-, di-, monosaccharides, and polyols (LFD) has been shown to effectively reduce irritable bowel syndrome (IBS) symptoms. Effects resulting from real-world studies may differ from those seen in efficacy studies because of the diversity of patients in real-world settings. This systematic review and meta-analysis aimed to compare the effect of the LFD on reducing IBS symptoms and improving the quality of life (QoL) in efficacy trials and real-world studies.
Methods: Major databases, trial registries, dissertations, and journals were systematically searched for studies on the LFD in adults with IBS. Meta-analysis was conducted using a random effects model with standardized mean differences (SMD) and 95% confidence intervals (CI). Outcomes of interest were all patient-reported: stool consistency, stool frequency, abdominal pain, overall symptoms, adequate symptom relief, IBS-specific QoL and adherence to the LFD.
Results: Eleven efficacy and 19 real-world studies were reviewed. The meta-analysis results for abdominal pain (SMD 0.35, 95% CI 0.16 to 0.54) and QoL (SMD 0.23, 95% CI -0.05 to 0.50) showed the LFD was beneficial in efficacy studies with no statistically significant results for stool frequency (SMD 0.71, 95% CI 0.34 to 1.07). Real-world studies found improvements in abdominal pain and QoL. Due to heterogeneity, no meta-analysis was done for stool consistency and overall symptoms. In these outcomes, results were mostly supportive of the LFD, but they were not always statistically significant.
Conclusions: The results of this systematic review and meta-analysis suggest the LFD improves outcomes compared to a control diet (efficacy studies) or baseline data (real-world studies). Because of diverse study designs and heterogeneity of results, a clear superiority of the LFD over control diets could not be concluded. There are no indications of an efficacy-effectiveness gap for the LFD in adults with IBS.

1. Introduction

Irritable bowel syndrome (IBS) is characterized by recurrent abdominal pain and altered bowel habits [1]. Adults with IBS typically suffer from various but individually different gastrointestinal and non-gastrointestinal symptoms resulting in reduced health-related quality of life (QoL), psychological distress, and impaired workforce productivity [2,3]. In an international online survey with a random population sample of 73,076 respondents, about 4.1% of the participants met the Rome IV criteria [4], the most recent diagnostic criteria for IBS.

Fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) are thought to be involved in IBS symptom development in a number of ways, such as increased luminal distension caused by gas and water, modulation of visceral hypersensitivity, and increased intestinal permeability [5]. A diet low in FODMAPs (LFD) includes three phases: restriction, reintroduction and personalization [6]. A number of systematic reviews has been confirmed that the LFD reduces IBS symptoms effectively [7–12]. Nonetheless, some authors have emphasized the need for further research [7–9], especially on the long-term efficacy and safety of the LFD [10–12].

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The most recent systematic reviews assessing the extent of symptom reduction by the LFD in adults with IBS were published in 2021 [11,13]. All three showed that the LFD had a greater effect in reducing IBS symptoms than habitual diet or control diets. Over a dozen new studies on the LFD in adults with IBS have since been published which warrants an updated systematic review. Furthermore, to our knowledge, no other systematic review so far has assessed whether the effects reported in efficacy studies differ from those seen in real-world studies. For example, two of the three recent systematic reviews only included randomized controlled trials assessing efficacy [11,13], whereas the third one also included intervention and observational studies but did not differ between different study types in their analysis [10]. Comparing the efficacy of an intervention to its real-world effectiveness is, however, relevant as efficacy studies tend to of overestimate an intervention's effect due to strictly defined study populations and procedures [14]. Real-world effectiveness may differ significantly from efficacy studies because of the diversity of everyday patients who frequently suffer from comorbidities, which would typically exclude them from efficacy-focused randomized controlled trials (RCT). The magnitude of this potential efficacy-effectiveness gap is not known for the LFD. In other medical fields, investigations on the extent of the efficacy-effectiveness gap have found a broad range of results. For example, the systematic review by Ankarfeldt et al. [15] revealed no indication of an efficacy-effectiveness gap on blood glucose-lowering drugs. However, they noted that this result may have been influenced by study limitations such as the number of included studies and bias related to the observational studies. In comparison, a meta-analysis on current systemic cancer therapies found that the median overall survival rate in real-world data was 5.2 months less than those reported in RCTs [16]. These findings suggest that the presence of an efficacy-effectiveness gap is dependent on the medical field.

To our knowledge, there has not yet been an investigation into the efficacy-effectiveness gap on the impact of the LFD on symptoms, though such a study is highly warranted. Therefore, this systematic review and meta-analysis aims to compare how effectively the LFD reduces IBS symptoms and improves QoL in efficacy RCTs and in real-world studies.

2. Materials & methods

The study protocol for this systematic review has been published [17] and was developed following the Cochrane Handbook for Systematic Reviews of Interventions version 6.1 [18] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) reporting guidelines [19]. The review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in November 2021 (registration number: CRD42021278952). The *United States Food and Drug Administration (FDA) for Industry: Irritable Bowel Syndrome – Clinical Evaluation of Drugs for Treatment* guidance [20] was used to define the outcomes of interest.

2.1. Eligibility criteria

To address the aim of this study, two sets of eligibility criteria were developed, both structured as population, intervention, comparison, outcomes and study design (PICOS) categories. The first PICOS focused on efficacy studies (efficacy PICOS), and the second on results from real-world settings (real-world PICOS). The publication date was not restricted. The publication language was limited to English, German, French and Italian due to practicality. Studies had to be published as a full manuscript or authors had to provide all relevant information. The defined population was human adults with IBS who were representative of the typical population group in efficacy studies for the efficacy PICOS. For the real-world PICOS, the population was typical adults with IBS in everyday practice. For this differentiation, we developed a rating system based on the 'eligibility' domain of the Pragmatic Explanatory Continuum Indicator Summary Tool (PRECIS-2), which also ensured that no study was included in both PICOS [17,21]. The efficacy PICOS participants had to present with clinically relevant baseline outcomes scores. The intervention groups had to follow the LFD for at least four weeks in both PICOS; the combination of the LFD with placebo was also allowed. As a control intervention, other dietary interventions for IBS (also for at least four weeks) could include other diets, probiotics, fiber supplements or combining the LFD with other substances. No control group was required for the real-world PICOS. The outcomes were divided into critical outcomes, which included stool consistency, stool frequency, abdominal pain, and important outcomes, such as overall symptom scores, adequate symptom relief, IBS-specific QoL and adherence to the LFD. The study design was limited to RCT for the efficacy PICOS. Prospective or retrospective designs, including audits, were accepted for the real-world PICOS, but not case reports and qualitative studies.

2.2. Search strategy and study selection

The search was conducted in March 2021 by LC and NB and updated in May 2022 by SJ. The databases EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials, CINAHL, trial registries (ClinicalTrials.gov, WHO-Portal International Clinical Trial Registry Platform), unpublished dissertations (LILACS, Open Access Theses, and Dissertations, ProQuest Dissertation & Theses Global) and grey literature (Grey Matters, Open Grey) were searched. Additionally, 12 relevant journals were hand searched individually.

The search terms included 'FODMAPs' and 'IBS' (combined with AND), as well as synonyms and the MESH term for IBS (no MESH term for FODMAPs existed at the time the study protocol was developed, Table S1). No restrictions were applied during the search (e.g., study design) to avoid missing any eligible studies. The search was conducted once for both of the PICOS groups together.

Search results were imported into Covidence (Veritas Health Innovation Ltd), where duplicates were automatically removed. Study selection, data extraction and quality assessment were done by a team of reviewers (NB, GST, LC, SJ), with each study being assessed by two reviewers independently. Inconsistent judgements were indicated by Covidence and resolved by the two reviewers and SJ rechecking the information in the publication(s).

Because of the two PICOS groups, the title and abstract screening were done in two rounds (Fig. 1). In the first round, all the non-eligible studies for both PICOS were eliminated (e.g., narrative reviews, FODMAP content analysis, pediatric studies, and studies on disorders other than IBS). The second round of title and abstract screening and subsequent full-text evaluation were done separately for both PICOS groups.

2.3. Data extraction

Data extraction included general information on the studies, baseline characteristics and data on the prespecified outcomes. There was no restriction on how the predefined outcomes were measured. Data were extracted for baseline, post FODMAP elimination, post FODMAP reintroduction, and at the end of follow-up, including change scores (e.g., from baseline to post FODMAP elimination).

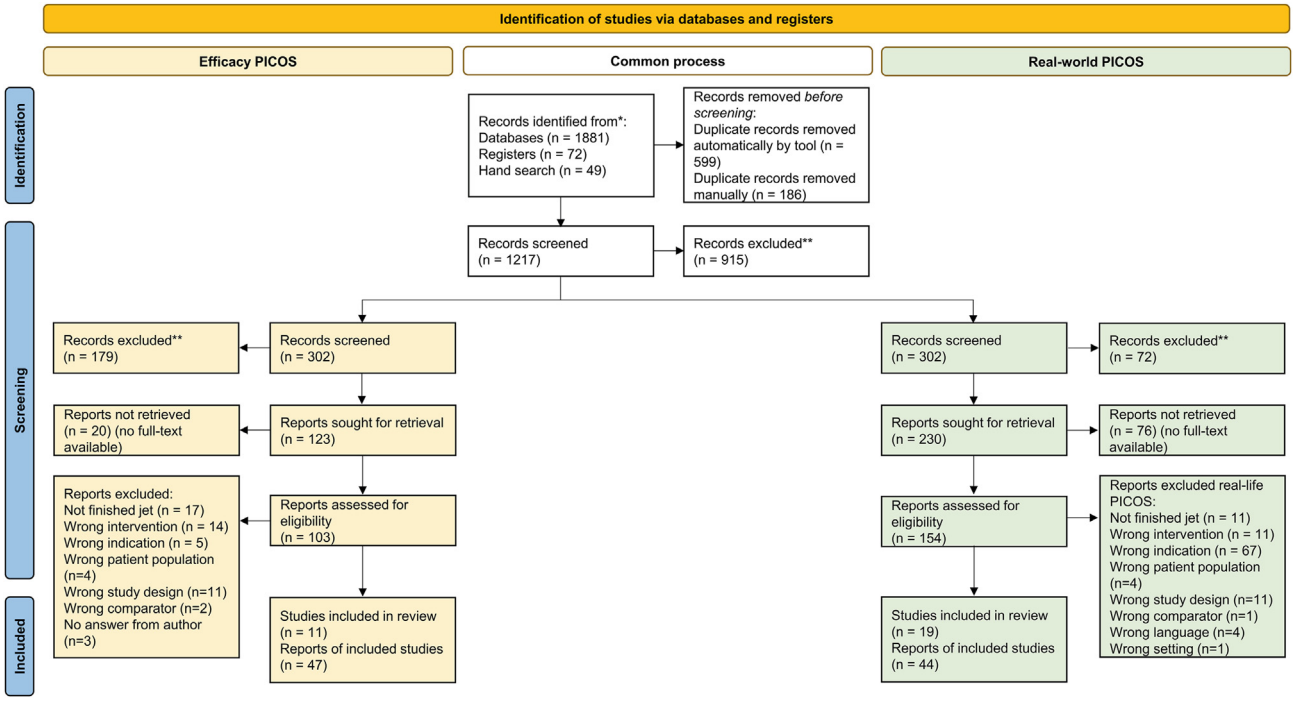

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for literature search and study selection.

2.4. Risk of bias and quality assessment

Several risk of bias tools were used to account for different study designs (NB, GST) [18]. These included the revised tool for Risk of Bias in randomized trials (RoB 2) [22], the newly available test version of RoB2 for crossover studies [23], and the Risk of Bias in non-randomized Studies – of Interventions tool (ROBINS-I) for non-randomized studies [24]. For quality assessment, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system's following criteria were used: indirectness of evidence, imprecision, large magnitude of an effect, the effect of plausible residual confounding (KSE, MR) [25].

2.5. Data analysis

Data were transferred from Covidence to Excel for data analysis. Meta-analyses were done in Review Manager version 5.4 (Cochrane Collaboration), the risk of bias figures were produced with robvis [26]. Since the outcome data were considered sufficiently similar between studies, we performed meta-analyses for some outcomes of the efficacy PICOS, contrary to this study's protocol [17]. Change scores were used because of the clinically relevant differences in baseline values. The predefined subgroups [17] for analysis were not applied because of insufficient studies for the subgroups. Most studies reported the results at least partly using a per protocol (PP) analysis. Therefore, results based on intention-to-treat (ITT) or PP analysis were included but separated into two subgroups in the meta-analysis. If data were not presented as a change mean and a change standard deviation (SD), these were calculated using the Review Manager 5.4 calculator or based on the Cochrane handbook for systematic reviews [18]. As a third option, SD change was calculated based on SDbaseline and SDpost [18] with a value of 0.7 for r as a conservative estimate [18,27,28]. Stool data were measured on scales which were difficult to compare. Therefore, the data were transformed to "difference from optimum" at baseline and follow-up and a change-value was calculated. For example, the optimum was defined as a 4 on the Bristol Stool Form Scale or a 0 on a visual analog scale, where 0 was defined as no disturbance. For stool frequency, the optimum was defined as one bowel movement per day. Although the definitions were relatively rigid, they facilitated determining if outcomes changed in the right direction.

Continuous data were reported as "standardized mean difference" with 95% confidence intervals (CI). Based on the study protocol [17], we intended to report results as mean difference if the same measures were used. However, this was only the case for IBS-related QoL. One real-world PICOS study interpreted lower scores as improvement [29], so the standardized mean difference of IBS-related QoL in both PICOS was used for consistency. In studies without a control group, we used baseline data as a comparison. Dichotomous data, such as adequate symptom relief questions (e.g., "over the past X days, do you feel that you have had adequate relief of your IBS symptoms?") were reported as risk difference with 95% CIs. In studies without a control group, data were presented as a percentage of participants reaching adequate symptom relief.

Because of the heterogenous control diets, meta-analyses was only done if there was no was evidence for considerable heterogeneity (I^2 over 75% in at least one analysis [30]). Otherwise, data were shown as forest plots without meta-analysis. This was also the case if data were available only for one study per subgroup, or in the real-world PICOS studies were baseline data was compared with post-intervention outcomes.

3. Results

From a total of 2,002 records identified, 47 records reporting on 11 studies were included in the efficacy PICOS and 44 records reporting on 19 studies were included in the real-world PICOS (Fig. 1). Some studies seemed to meet the inclusion criteria but still had to be excluded, usually because the studies' populations were rated as efficacy populations in the PRECIS-2-based rating but other efficacy PICOS eligibility criteria were not met [31–33], or the data analysis was based on groups not compatible with the inclusion

criteria, e.g. if the results of responders were compared with non-responders [34].

Most studies assessed with the RoB 2 tool (all efficacy PICOS studies and four real-world PICOS studies) were rated as having "some concerns", with one efficacy PICOS [35] and one real-world PICOS study [36] rated as high risk (Figs. S1 and S2). The "high risk" efficacy PICOS study could only be included in the analysis of abdominal pain and overall symptoms [35] and the "high risk" real-world study only in the analysis for abdominal pain and IBS-related quality of life [36]. Studies rated with the ROBINS-I tool were largely assessed as having a serious risk rating, with one study [29] rated as low risk and one [37] with moderate risk (Figs. S3 and S4). Results of the study rated as having a low risk of bias were included in the analysis for overall symptoms and IBS-related quality of life [29] and those of the study rated as moderate risk in the assessment of adequate symptom relief and adherence [37]. In the GRADE assessment, efficacy PICOS studies were found to have moderate quality of evidence (Table S2), whereas the real-world PICOS studies had very low quality of evidence (Table S3).

Covidence calculated Probability of Agreement and Cohens Kappa as 0.65 and 0.39–1 for title and abstract screening, 0.89–1 and 0.68–1 for full text screening in the efficacy PICOS. In the real-world PICOS, the Probability of Agreement and Cohens Kappa were 0.71–1 and 0.33 for title and abstract screening and 0.78.-1 and 0.82.-1 for full text screening.

3.1. Study characteristics

Study characteristics are shown in Tables S4–S7. Based on the inclusion criteria, all studies included in the efficacy PICOS were RCTs (n = 11) [35,38–47]. In the real-world PICOS, four randomized controlled trials [36,48–50], nine prospective studies [37,51–58], two pilot studies [29,59], two service evaluations [60,61], and two retrospective studies [62,63] were included. In most studies, the majority of participants were female (Tables S4–S7). In the efficacy PICOS studies, the percentage of female participants ranged from 42% to 86%, with four studies including less than 55% females [40,42,46,47] and seven studies having more than two thirds of their sample as females [35,38,39,41,43–45]. There were 42%–89% females included in the real-world PICOS studies. The samples of two prospective studies [55,56] and one pilot study [59] included less than two thirds of female participants and one study did not report the percentage of female participants for the IBS subgroup [60]. Some studies reported baseline values for anxiety symptoms (mostly measured with the Hospital Anxiety and Depression Scale) [38,43,44,47,48,50,53,57]. The mean values of the anxiety scale were mostly near or in a range commonly considered as "potential case". Therefore, a high percentage of the participants may have suffered from some anxiety symptoms. However, studies also assessing outcome anxiety data did not find significant differences between responders and non-responders or the response rate to the dietary intervention [38,39], no negative or even a positive effect of the interventions on anxiety [41,44,48,50,57] and a reduced number of participants taking anxiety medications [40].

Most efficacy PICOS studies [38–42,45–47] but no real-world PICOS studies assessed adverse events. When reported, they were not serious (e.g., nausea, worsened gastrointestinal symptoms). There were no significant differences in participants with adverse events between study groups, therefore, the adverse events unlikely impacted the study results.

The studies were conducted in countries spread over four continents. In the efficacy PICOS, there were n = 6 in Europe [35,38,41,44–46], n = 4 in Asia [40,42,43,47], and n = 1 in America [39] and in the real-world PICOS, there were n = 13 in Europe [29,37,48,49,49,52–56,58,61–63], n = 5 in Australia and Oceania [36,50,51,57,60], n = 1 in Asia [59]. Efficacy PICOS studies included between n = 34 and n = 110 participants and real-world PICOS between n = 16 and n = 233 participants. Mean age ranged between 34.1 years and 51 years in the efficacy PICOS and 34.6 years to 54.9 years in the real-world PICOS.

In the efficacy PICOS, the intervention duration was between 4 and 12 weeks. Only one study comparing the LFD with a standard IBS diet in adults with IBS-Diarrhea reported results post the FODMAP reintroduction [40]. The most common control group was a standard IBS diet [38–40,43,44,47]. Other comparisons were a sham diet [45,46], probiotics [45], an ayurvedic diet [41], a LFD plus gluten [42], or a diet replacing cereals with tritordeum-based foods (Tritordeum-based diet) [35]. The results of studies using one of these "other" control diets could only be included in the analysis of overall symptoms and adequate symptom relief [45], or adequate symptom relief and adherence for the sham diets [46], the analysis of abdominal pain, overall symptoms, IBS-related quality of life, and adherence for the Ayurvedic diet [41], and the analysis of abdominal pain and overall symptoms for the Tridordeum-based diet [35].

In the real-world PICOS, most studies did not include a control group [29,51–63]. Only the RCTs and one prospective study had a control group, with control interventions being probiotics [48], a normal Danish diet [48], gut-directed hypnotherapy [50], the LFD combined with a fructooligosaccharide supplement [49], a standard IBS diet [37], or adults with IBS on a waiting-list [36].

3.2. Abdominal pain

Nine efficacy PICOS studies with 604 participants were included in the meta-analysis on changes in abdominal pain from baseline to post FODMAP elimination (Fig. 2) [38–40,42–44,47]. The IBS Symptom Severity Scale (IBS-SSS) subscale was used most frequently to assess abdominal pain and these results were used for the analysis where available [35,38,40,42,44,47]. Additionally, abdominal pain was also assessed with a visual analog scale [43] or a question on improvement of abdominal pain using a five-point Likert scale [41]. The LFD has better results for all point estimates, but in most studies, the pooled effects indicated a statistically significant advantage for the LFD over the control diets in the overall analysis (0.35, 95% CI 0.16 to 0.54, I^2 28%, Chi^2 11.05) and the PP subgroup (0.42, 95% CI 0.16 to 0.69, I^2 38%, Chi^2 8.01), but the standardized mean difference was not statistically significant in the ITT subgroup (0.20, 95% CI -0.07 to 0.47, I^2 0%, Chi^2 1.25) (Fig. 2). There was no clear indication of differences between studies with and without statistically significant effects. For example, studies with statistically significant effects only included IBS-Diarrhea subjects [39,47], but this was also the case for some studies with statistically nonsignificant effects [35,40].

Post-FODMAP-reintroduction results showed a reduction of abdominal pain − compared to baseline and measured with the IBS-SSS subscale − of 22.1 (±19.3) for the LFD and 19.3 (±18.3) for the standard IBS diet and a reduction of 27.8 (±25.6) for the LFD and 26.1 (±18.8) for the standard IBS diet from baseline to post FODMAP-elimination [40].

In the real-world PICOS, the results of two RCTs [36,50], four prospective [51,52,57,58] and one retrospective studies [62] with 409 participants could be included in the analysis of abdominal pain. Abdominal pain was measured with the IBS-SSS subscale [36,52], a subscale of the Gastrointestinal Symptom Rating Scale [51,57], a 4-point [62] or 11-point [58] Likert scale or a visual analog scale [50]. The outcomes improved statistically significantly from baseline to all reported time points in all studies with the LFD. However, some of the CI were quite wide, which indicates uncertainty in the results (Fig. 3).

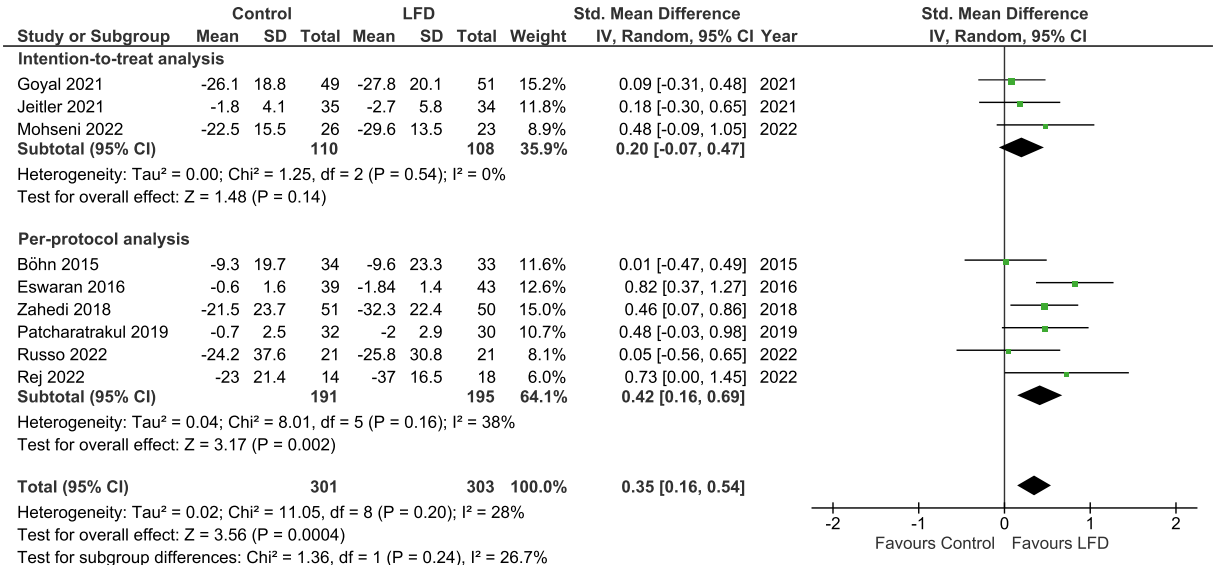

Fig. 2. Change in abdominal pain, efficacy PICOS.

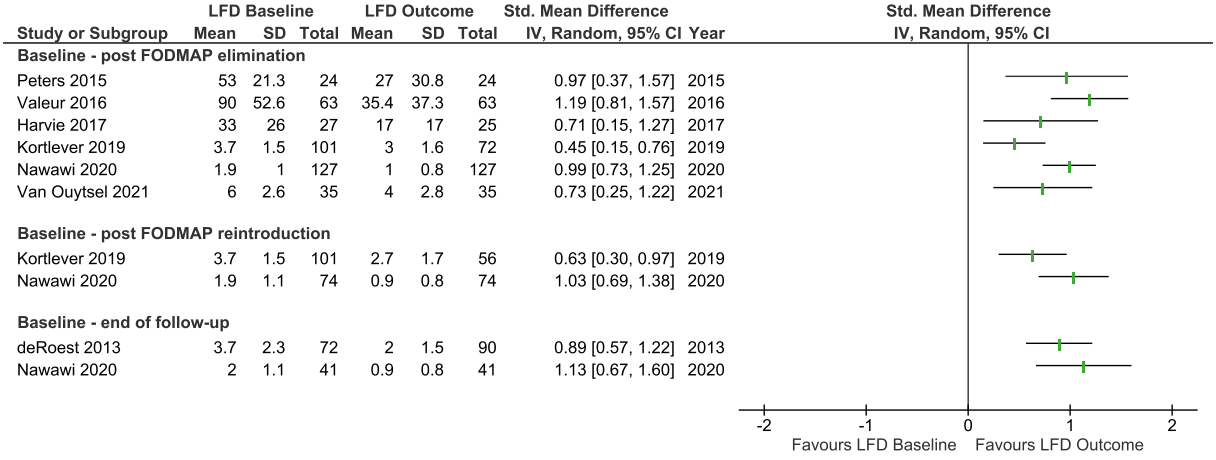

Fig. 3. Abdominal pain baseline – outcome, real-world PICOS.

3.3. Stool consistency

Five randomized controlled trials (RCT) with 399 participants were included in the post FODMAP elimination analysis of stool consistency in the efficacy PICOS [38–40,42,47]. Stool consistency was generally measured with the Bristol Stool Form Scale [38–40,47,64]. One study used a visual analogue scale [42]. The meta-analysis showed evidence for considerable heterogeneity in the intention-to-treat (ITT) subgroup (I^2 98%, Chi^2 46.65) and the overall analysis (I^2 94%, Chi^2 69.78), and evidence for moderate heterogeneity in the PP subgroup (I^2 41%, Chi^2 3.37). Therefore, the results in Fig. 4 are shown without meta-analysis. All point estimates support the LFD over the control diet, but in one of two ITT comparisons and two of three per protocol (PP) comparisons this was not statistically significant (Fig. 4). Different population groups may potentially explain the heterogeneity between in both subgroups, as the studies with statistically significant effects for the LFD included only IBS-diarrhea patients [39,40,47], whereas the other studies included patients from all IBS subtypes [38,42].

The study reporting post FODMAP reintroduction data measured stool consistency with the Bristol Stool Form Scale. The difference from optimum changed from 2.13 (±0.69) for the LFD and 2.24 (±0.64) for the standard IBS diet at baseline to 0.37 (±0.51) and 2.01 (±0.65) post FODMAP elimination and 0.82 (±0.71) and 2.16 (±0.82) post FODMAP reintroduction [40].

Real-world studies rarely reported results on stool consistency. Therefore, the results are reported narratively. In a RCT using a visual analogue scale, stool consistency in the LFD group improved by 42 point (95% CI -54 to −29) post FODMAP elimination and by 34 points (−47 o −22) post FODMAP reintroduction [50]. A retrospective cohort study (n = 127) assessed the stool consistency with the Bristol Stool Form Scale. Post FODMAP elimination, 61% (n = 24) patients originally reporting diarrhea-type stool consistency (types 5–7 on the Bristol Stool Form Scale, n = 61) and 47% (n = 24) of those reporting constipation-type stool consistency (types 1–2, n = 45) reported normal stool consistency (types 3–4) [62]. De Roest et al. [51] used a prospective study design (n = 90) and assessed stool consistency with a seven-point Likert scale. At end of follow-up, they reported an improvement (at least two points) of hard stools in 52.4% (n = 22) and constipation in 38.5% (n = 20) of the participants reporting these symptoms at baseline. Rates of improvement in loose stools and diarrhea were 53.4% (n = 31) and 59.6% (n = 28), respectively.

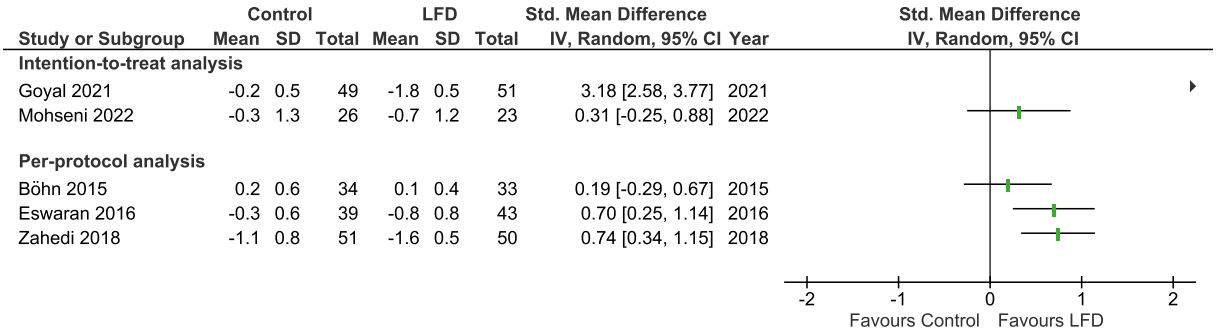

Fig. 4. Change in difference from optimum in stool consistency, efficacy PICOS.

3.4. Stool frequency

The results on stool frequency are again reported as change in difference from optimum. Six efficacy PICOS studies with 461 participants were included in the analysis of stool consistency. Stool frequency was assessed as times bowels opened per day [38–40,47], or per week [43] or with a visual analog scale [42]. The majority of studies reported a statistically significant improvement in stool frequency on the LFD compared with the control diet (Fig. 5). However, one study reported a positive but statistically nonsignificant effect for the control diet (−0.10; −0.59 to 0.40) [43]. Accordingly, the heterogeneity tests showed evidence for homogeneity in the ITT subgroup (I^2 0%, Chi2 0.00), but evidence for substantial heterogeneity in the PP subgroup (I^2 68%, Chi^2 9.36) and the overall analysis (I^2 72%, Chi^2 18.01). Studies with the largest effects reported ITT results and included adults with IBS based on Rome IV criteria [40,42]. The study with results supporting the control diet was the only study in which gastroenterologists instructed adults with IBS and not dietitians/nutritionists [43].

The difference from optimum in stool frequency was 2.91 (±1.21) for the LFD and 2.78 (±1.42) for the standard IBS diet at baseline, 1.11 (±0.91) and 2.12 (±0.91) post FODMAP elimination and 1.52 (±1.14) and 2.34 (±1.11) post FODMAP reintroduction [40].

In the real-world PICOS, the stool frequency analysis included one prospective [54] and one retrospective study [63]. Both studies dichotomized the stool frequency as normal (every three days to three times daily) and abnormal. The percentage of reported abnormal stool frequency was reduced from 21% to 7% [54] and from 33% to 14% [63]. The risk difference of both studies supports the LFD and the 95% CI did not include zero (Fig. 6).

3.5. Overall symptoms

Nine efficacy PICOS studies with ten comparisons and 623 participants reported overall symptom scores, mostly using the IBS-SSS [35,38,40–42,44,45,47] and one study using a visual analog scale [43]. The tests for heterogeneity showed evidence for considerable heterogeneity in the ITT subgroup (I^2 83%, Chi^2 24.19) and overall analysis (I^2 77%, Chi^2 39.05), and evidence for substantial heterogeneity in the PP subgroup (I^2 72%, Chi^2 14.42). Therefore, the results in Fig. 7 were not shown as meta-analysis. Most studies reported effects supportive of the LFD, with three PP studies with statistically nonsignificant effects [35,38,44] (Fig. 7). One ITT study reported better effects with the control diet [41], which greatly impacted the heterogeneity tests results. After the removal of the Jeitler et al. study [41], heterogeneity in the ITT subgroup was I^2 0%, Chi^2 1.88. This study was the only one comparing the LFD to an Ayurvedic diet. Furthermore, it included a long FODMAP elimination period (12 weeks), had different diagnostic criteria (S3 guideline from Germany [65]) and a non-inferiority study design. Differences explaining heterogeneity in the PP subgroup were less clear.

In the study assessing post FODMAP reintroduction data, IBS-SSS scores were reduced by 135.2 (±96.8) for the LFD and 81.4 (±87.62) for the standard IBS diet post FODMAP elimination and 109.9 (±95.22) and 65.7 (±91.6) post FODMAP reintroduction.

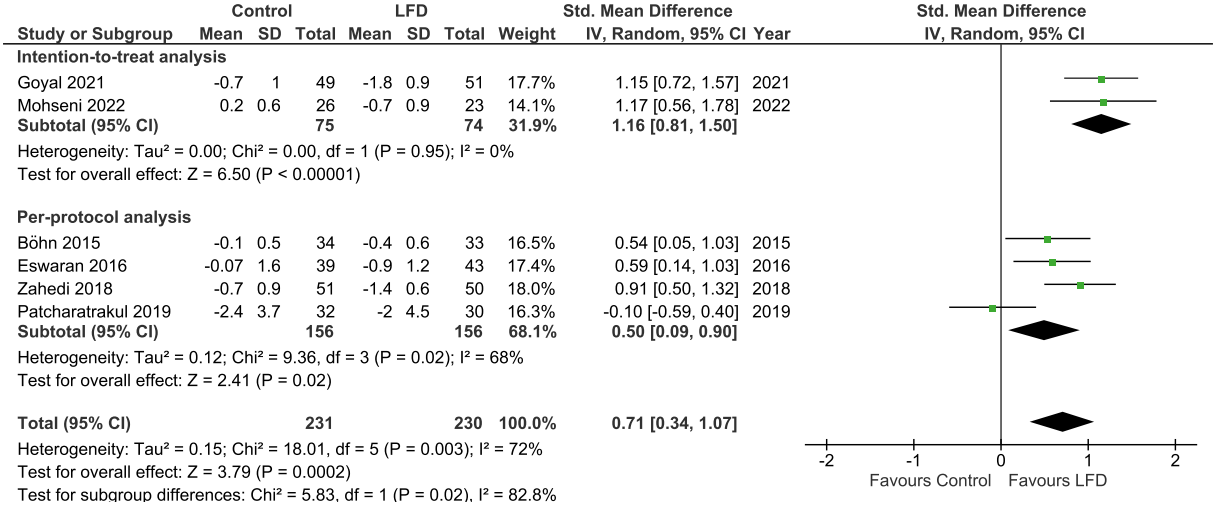

Fig. 5. Change in difference from optimum in stool frequency, efficacy PICOS.

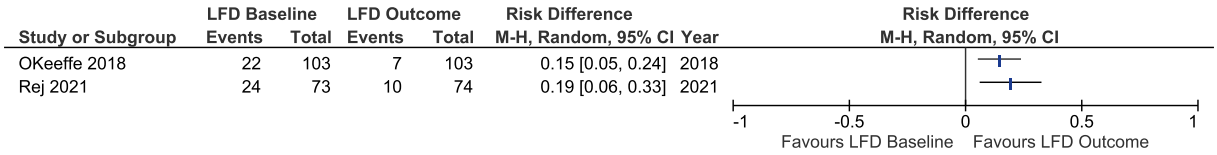

Fig. 6. Percentage of abnormal stool frequency, end of follow-up, real-world PICOS.

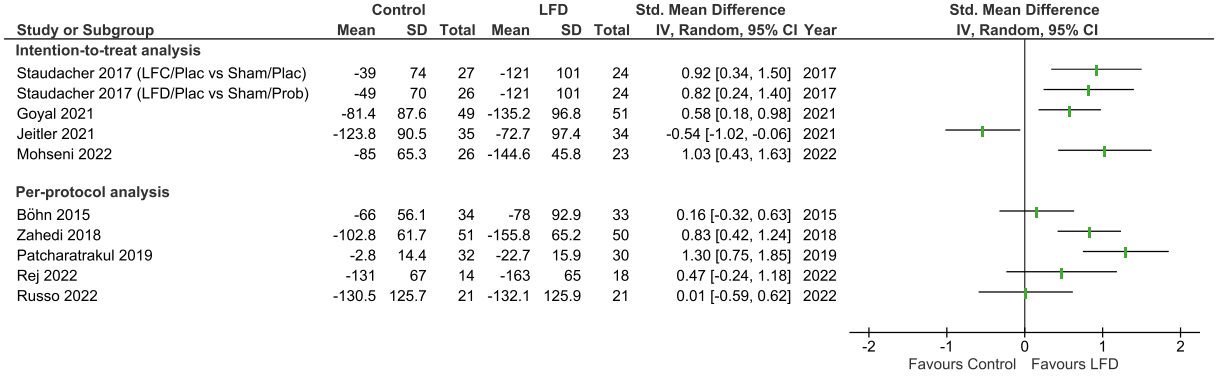

Fig. 7. Change in overall symptoms, efficacy PICOS.

The real-world overall symptom analysis included four studies with a prospective study design [52,53,55,57], one retrospective [62], and one pilot study [29] with 599 participants (Fig. 8). Overall symptoms were measured with the IBS-SSS [29,52,53,55], the Gastrointestinal Symptom Rating Scale [57] or a 4-point Likert scale [62]. All studies show a statistically significant effect of the LFD. The extent of the effect, however, varied between studies. Studies with fewer participants tended to report better outcomes with a wider 95% CI.

3.6. Adequate symptom relief

Three efficacy PICOS studies reporting four comparisons with 157 participants were included in the analysis on adequate symptom relief [39,45,46]. Three comparisons supported the LFD, but these effects were all not statistically significant (Fig. 9). When the LFD was compared with a sham diet plus probiotics, there was no difference between the two groups.

Two real-world PICOS studies with a non-controlled prospective study design and 145 participants reported dichotomous results on an adequate symptom relief question [37,54]. Post FODMAP elimination, 76 % of the participants (32/42) [37] and 61% (63/103) [54] reported adequate symptom relief, and 57% (59 of 103) did so at end of follow-up [54].

3.7. IBS-related quality of life

Six efficacy PICOS studies with 433 participants were included in the IBS-related QoL analysis [39–42,44,47]. All studies measured the IBS-related QoL with the IBS-QoL Instrument [66]. One ITT study showed a positive but statistically nonsignificant effect for the control diet [41]. All results of the other studies showed positive effects for the LFD, but most were not statistically significant (Fig. 10). The results showed a high degree of uncertainty as the 95% CI of the subtotals and the total of the meta-analysis were quite wide. The tests for heterogeneity show evidence for moderate

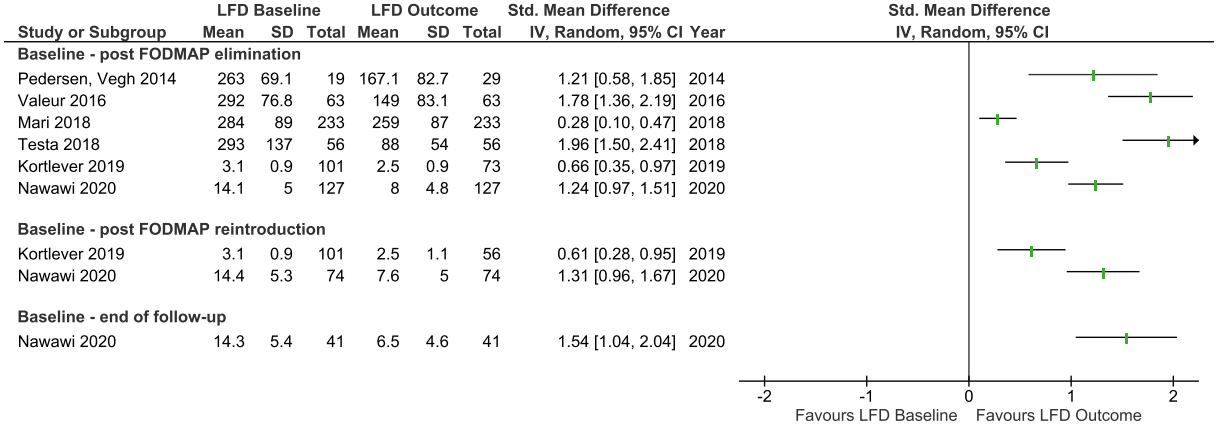

Fig. 8. Overall symptom scores, baseline − outcome, real-world PICOS.

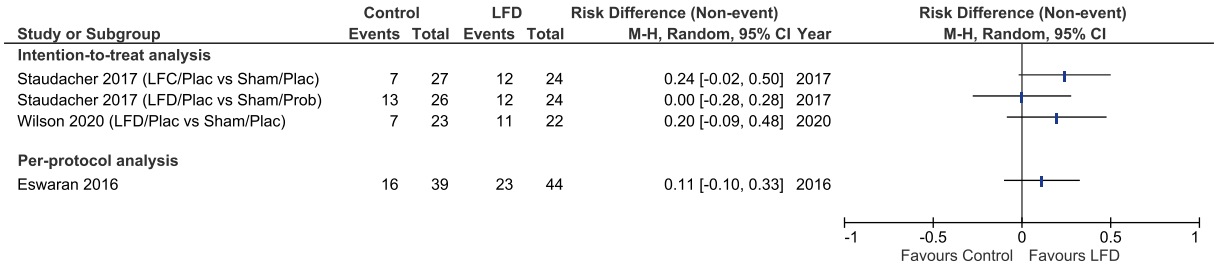

Fig. 9. Adequate symptom relief question, efficacy PICOS.

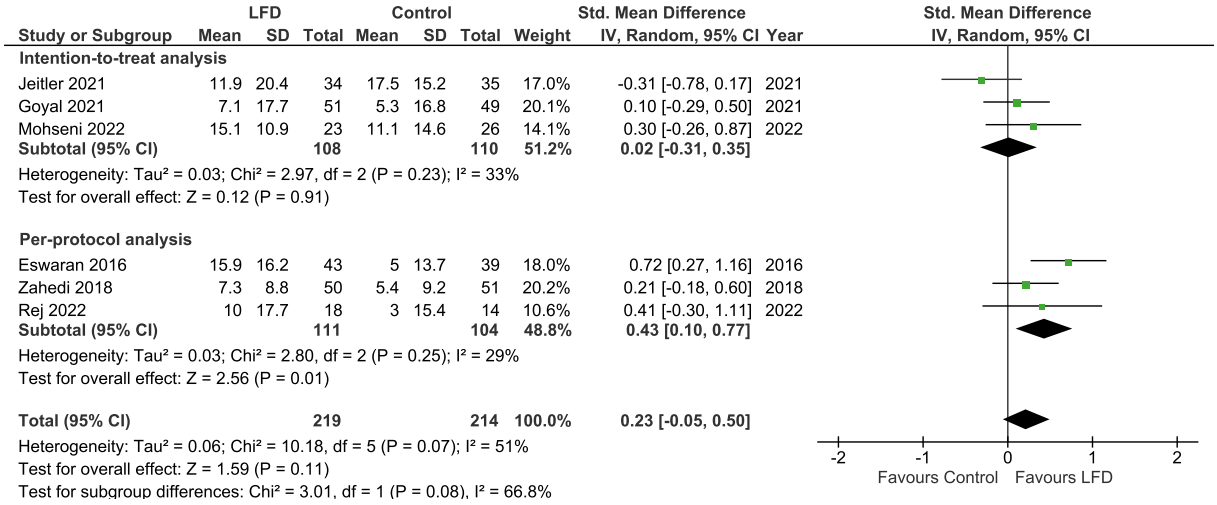

Fig. 10. Change in IBS-related quality of life, efficacy PICOS.

heterogeneity in the subgroup (ITT I^2 34%, Chi^2 3.02, PP I^2 67%, Chi^2 5.99) and the overall analysis (I^2 53%, Chi^2 10.68). The study indicates that negative effects on the IBS-related QoL were characterized by comparing the LFD to an Ayurvedic diet, different criteria to determine IBS (S3 guideline from Germany) and being a non-inferiority study [41].

In the study that also assessed post FODMAP reintroduction data, IBS-related QoL increased by 7.1 (±17.7) for the LFD and 5.2 (±16.8) for the standard IBS diet from baseline to post FODMAP elimination and by 14.1 (±10.5) and 9.4 (±10.5) to post FODMAP reintroduction [40].

The IBS-related QoL analysis of real-world PICOS studies included one RCT [36], one prospective [57] and one pilot study [29] with 135 participants. The LFD had better results in all comparisons, but the results of one comparison post FODMAP elimination [29] and one post FODMAP reintroduction [36] were not statistically significant (Fig. 11). The study with a statistically nonsignificant post FODMAP elimination effect [29] was a pilot study, had the lowest number of participants (n = 19), was conducted in Europe as compared to the other two studies (conducted in Australia & Oceania) and did not convert the IBS-QoL scores as the other two studies did.

3.8. Adherence

Adherence was assessed via nutrient intake or adherence-related questions. These results are presented in the supplementary file.

4. Discussion

In summary, the results in both RCT and real-world PICOS groups suggest that LFD improves outcomes more than control diets (efficacy PICOS) or compared to baseline data (real-world PICOS) but do not show a clear superiority of the LFD. Symptom reduction seems to be sustained in the long-term, but data on long-term effects remain scarce. There was no indication of an efficacy-effectiveness gap when the LFD is used by adults with IBS.

The current study found short-term positive effect results of the LFD on IBS symptoms and QoL in adults with IBS, which are in line with other systematic reviews and meta-analyses [11,12,67,68]. For example, a network meta-analysis of 13 RCTs showed that the LFD ranked first compared to a standard IBS diet, sham diet, or alternative dietary approaches for overall symptom improvement, abdominal pain, and abdominal bloating, but the relative risk of overall symptoms not improving was 0.67 (95% CI 0.48 to 0.91, P-score = 0.99) [11]. Similarly, a network meta-analysis including six studies showed that the LFD resulted in a risk ratio of overall symptom reduction of 0.69 (95% CI 0.54 to 0.88; I2 = 25%) compared to alternative diets, high FODMAP diets, usual diet or LFD plus placebo [67].

The long-term results found in the current study showed a generally sustained improvement for all outcomes compared to baseline in efficacy and real-world PICOS studies post FODMAP reintroduction and at the end of follow-up. A few other recent studies also showed maintenance of symptom improvement. For example, studies by Staudacher et al. [69] and Seamark et al. [61] reported a 50% or more symptom improvement among participants

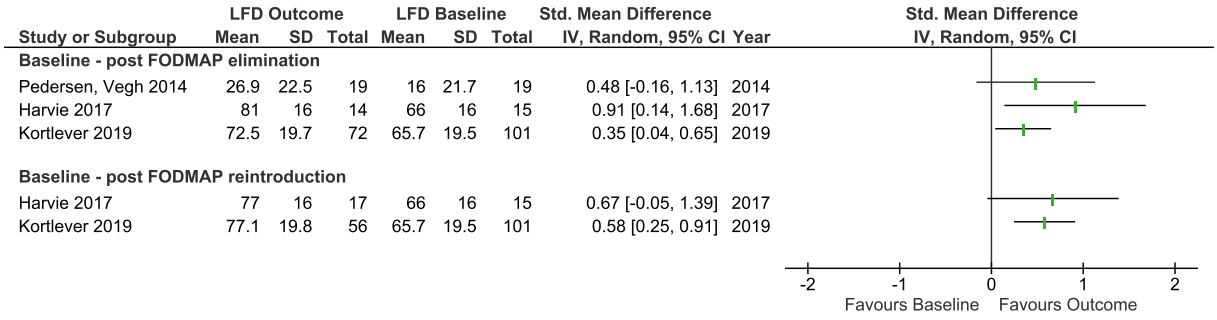

Fig. 11. IBS-related quality of life, baseline − outcome, real-world PICOS.

who followed an individualized LFD after almost one year. In a retrospective cross-sectional study (n = 90), less abdominal pain was associated with partial adherence to a LFD, which after nearly two years was reported by almost 80% of the participants [70].

The results of this systematic review and meta-analysis show no indication of an efficacy-effectiveness gap for the LFD in adults with IBS. The efficacy-effectiveness gap has been described as a result of greater variations in biological (e.g. patient characteristics), environmental (e.g., health care system characteristics), and behavioral factors (e.g., prescribing behavior and adherence) in real-world studies compared to efficacy RCTs [14,71]. For example, the broader defined eligibility criteria of real-world studies often result in study samples including more participants of older age, female gender, with more comorbidities and more severe baseline symptoms [72]. Interventions may be delivered in a broader range of settings by less specialized health professionals, and patients may adhere less to the intervention in real-world settings [14,71]. The results of this systematic review and meta-analysis could mean that no such gap exists for the LFD in adults with IBS or that the study samples and participant behavior differed less than expected between efficacy PICOS and real-world PICOS studies [14,71]. The latter may be the case, as despite differences in the eligibility criteria seen between studies included in the two PICOS (mostly upper age limit of 65 or 70 years, stricter symptom severity and comorbidity criteria in the efficacy PICOS studies), such clear differences cannot be determined in study populations' characteristics based on the data published. For example, the mean ages reported were in the same range for both PICOS (efficacy PICOS studies 34.1 to 51.0 years, real-world PICOS studies 34.6 to 49.0 years). Mean baseline symptom severity scores in studies reporting overall symptoms using the IBS-SSS were in a similar range in both PICOS (efficacy PICOS studies 242−318 (n = 7) [35,38,40−42,44,47], real-world PICOS studies 252−320 (n = 6) [29,36,48,52,53,55]). Differences in comorbidities could hardly be investigated as only 5 of 19 real-world PICOS studies reported information on comorbidities. However, in these studies, there was some indication that the study population included participants usually not suitable for an efficacy RCT, for example, participants with prior abdominal surgery [48] or suffering from other gastrointestinal diseases [62]. As for behavior, studies assessing adherence showed reasonable to very good compliance without indication of differences in adherence between efficacy PICOS and real-world PICOS studies.

This study was the first to systematically review how effectively the LFD reduces symptoms and improves the QoL in efficacy RCTs and in real-world studies. However, this systematic review and the included studies have some limitations. First, the variety of outcome measurement instruments and reporting, especially in the real-world PICOS studies, introduced uncertainty in the results. For example, abdominal pain was often measured with the current severity of abdominal pain subdomain of the IBS-SSS. However, some studies used visual analog, others numeric rating or Likert scales. Validation information about these scales was mostly missing and the respective questions were not described in detail. Therefore, the validity and aspects of abdominal pain assessed could vary considerably between outcome measurement instruments. Data on stool consistency were mostly reported as a mean of the Bristol Stool Form Scale. As a result, in studies including adults with different IBS subtypes, data with different directions representing an improvement (for IBS-Diarrhea a change from type 1 to type 3, but for IBS-Constipation a change from type 7 to type 5) were combined to a single mean value making interpretation difficult. Reporting such data dichotomously as normal/abnormal defecation as recommended in the FDA guidance for the clinical evaluation of drugs for the treatment of IBS [20] would increase transparency about improvements in stool consistency.

The differentiation between study populations representing "typical efficacy populations" and "usual patients in everyday practice" was complex. To differentiate between these two types of study populations, a system based on the eligibility domain of the PRECIS-2 tool [21] was developed, pretested with some studies and then applied to the RCTs included in the systematic review. This approach had its limitations, as we only used one of the nine domains, the PRECIS-2 tool was developed for design decisions and not for retrospective analysis, and a tool representing a continuum between explanatory and pragmatic studies had to be used dichotomously (typical "efficacy" or "usual" patients). Furthermore, as described by other authors [73], there was some uncertainty whether or not the information published represented all information required for a proper judgment. However, other researchers have also successfully applied the categorization and retrospective use of the PRECIS-2 tool [74,75]. Overall, the rating and the threshold applied in this study resulted in a clear difference in eligibility criteria, but as discussed above, this may not have translated into different study sample characteristics.

To assess the study question, we had to include a wide range of study designs. This may have introduced bias, which is represented by the risk of bias and the GRADE assessment yielding more serious risks of bias and lower confidence in the quality of evidence in the real-world PICOS studies. The larger sample sizes in most of the real-world studies as opposed to the RCTs have probably somewhat reduces this. However, the real-world PICOS studies also used more diverse and sometimes poorly reported outcome measurement methods. We accounted for this uncertainty by not conducting meta-analyses on the real-world data.

Finally, some RCTs (even in the efficacy PICOS) reported results of PP analysis, which violates the principle of randomization, and may have led to overestimating the effect of the interventions as those participants dropping out may have had more severe symptoms [76].

5. Conclusion

The results of this systematic review and meta-analysis confirm symptom improvement with the LFD in efficacy and real-world studies. There was no indication of an efficacy-effectiveness-gap when applying the LFD in adults with IBS. Studies reporting RCTs showed that the LFD resulted in better symptom improvement than control diets, but the LFD was not clearly superior. To substantiate similar analysis in the future, we recommend 1) that there should be an agreement on outcome measurement methods, 2) that dietitians should report real-world studies more often, preferably as full texts (not short publications) adhering to reporting guidelines whether this is required by the publishing journal or not, and 3) for journals to publish more real-world studies and give such studies adequate space to report enough information about the methods applied to allow meaningful analysis. In addition, it was found that data on the long-term outcomes of the LFD are still scarce. Such data is of great importance, since the effort of a restrictive three-phase diet, such as the LFD is only worthwhile if symptom relief persists. Therefore, more long-term efficacy and real-world studies on the LFD in IBS are warranted.

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Author contribution

SJ: conceptualization, methodology, formal analysis, investigation, writing – original draft, writing – review & editing, visualization, supervision, funding acquisition.

NB: methodology, formal analysis, investigation, writing – review and editing.

JH: writing – original draft, writing - review & editing.

LC, KSE, MR, LS, GST: investigation, writing – review & editing.

GR: conceptualization, methodology, writing – original draft, writing – review & editing, supervision.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

There are no conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.05.014.

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