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REVIEW

Probiotics therapy for adults with diarrhea-predominant irritable bowel syndrome: a systematic review and meta-analysis of 10 RCTs

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Abstract

Purpose Accumulating evidence showed that probiotics therapy might be effective in treating diarrhea-predominant irritable bowel syndrome (IBS-D). This study aimed to evaluate the effectiveness and safety of probiotics therapy for the treatment of IBS-D.

Methods We performed a comprehensive literature search in eight electronic databases, and gray literature from inception to August 4, 2021. Randomized controlled trials (RCTs) of probiotics therapy for the treatment of IBS-D were included and the quality was assessed using the risk of bias tool recommended by the Cochrane Handbook version 5.1.0. RevMan 5.4 software was used to perform the meta-analysis on the outcomes of IBS-D symptoms, abdominal pain, quality of life, and abdominal distension. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence.

Results Ten RCTs evaluating 943 patients were identified. Only one study had unclear risk of bias, while nine studies had a high risk of bias. The meta-analysis results showed that, compared to the placebo, probiotics therapy significantly decreased the score of IBS-D symptoms (SMD = −0.55, 95% CI: [−0.83, −0.27], $P < 0.05$), abdominal pain (SMD = −0.43, 95% CI: [−0.57, −0.29], $P < 0.05$), and abdominal distension (SMD = −0.45, 95%CI: [−0.81, −0.09], $P < 0.05$). There was no statistical difference in the quality of life. However, all the certainty of evidence was very low.

Conclusion Very low certainty evidence showed that probiotics might be an effective treatment for improving the IBS-D symptoms, abdominal pain, and abdominal distension, in adult IBS-D patients. However, these conclusions should be supported by high-quality evidence.

Keywords Diarrhea-predominant irritable bowel syndrome · Probiotics · Randomized controlled trials · Systematic review

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Introduction

Irritable bowel syndrome (IBS), characterized by typical symptoms, such as bloating, chronic abdominal pain, or discomfort along with altered bowel habits [1, 2], has over 23% prevalence worldwide and is one of the most common functional gastrointestinal disorders (FGIDs) [3]. Based on fecal characteristics, IBS is divided into four subtypes: constipation-predominant IBS (IBS-C), diarrhea-predominant IBS (IBS-D), mixed IBS (IBS-M), and unclassified IBS (IBS-U). IBS-D, the most common subtype of IBS, is characterized by frequent diarrhea accompanied by abdominal distension or abdominal pain [4] and accounts for approximately one-third of the total IBS cases [5]. This disease can severely affect and reduce the patient's quality of life and contribute to the economic burden on people [6–8].

Currently, the etiology and pathogenesis of IBS-D are still unclear. Relevant studies suggested that IBS-D was associated with the dysbiosis of the gut microbiota, visceral hypersensitivity, stress, genetics, diet, and psychosocial factors [9–11]. The currently available drugs for IBS-D include alosetron hydrochloride (5-HT3 antagonists), selective M3 receptor antagonists, loxiglumide, somatostatin, oxytocin, tachykinin, antispasmodics, antimotility drugs, and anti-depressants [12–16]. Besides, the treatment methods for IBS-D also include diet therapy and psychotherapy [17]. However, some medicinal treatments have side effects, such as constipation, nausea, headache, abdominal pain, bloating, and diarrhea [18, 19]. Therefore, it is essential to find novel treatment methods for IBS-D. Furthermore, increasing evidence suggested that the gut microbiota had a significant role in the pathophysiology of IBS [20–22].

Probiotics are viable microorganisms, which can prevent recurrent pouchitis and *Clostridioides difficile* diarrhea [23]. They can have beneficial effects on the host by intestinal mucosal barrier, increasing the antioxidant levels, promoting nutrient absorption, improving the body's immunity, and maintaining the balance of the gut microbiota [24]. To date, several clinical trials have been conducted to evaluate the efficacy of probiotics in IBS-D. Some clinical trials showed that probiotics could significantly relieve diarrhea and overall symptoms of IBS-D [19, 25]. Furthermore, several guidelines stated that probiotics might effectively relieve bloating, flatulence, and IBS symptoms [26–29]. A couple of guidelines indicated that the probiotics, consisting of *Lactobacillus*, *Bifidobacterium*, *Escherichia*, *Streptococcus*, or combination probiotics, had beneficial effects on the persistence of overall IBS symptoms [26, 27]. However, other trials have shown no effect of probiotics on individual symptoms, such as abdominal pain, abdominal distension, and stool frequency [18, 30, 31]. Numerous systematic reviews and meta-analyses, investigating the effects of probiotics on IBS patients, suggested that probiotics were beneficial for IBS patients [32–38]. Although these studies have certain limitations, each study has certain beneficial effects for IBS patients. However, the most effective species and strains are still uncertain due to differences in the study designs, such as study population, study methods, and duration of treatment, and dose and types of probiotics used. Moreover, systematic reviews or meta-analyses investigating the efficacy of probiotics in IBS-D are also lacking. Therefore, the current study was performed to assess the efficacy and safety of probiotics for the treatment of adult IBS-D patients.

Materials and methods

Literature search

Eight electronic databases, namely PubMed, Web of Science, The Cochrane Library, Embase, CNKI, CBM, VIP, and Wanfang Data, were searched as well as gray literature as a supplementary search to identify and collect RCTs on probiotics therapy for IBS-D, all from the time of database inception to August 4, 2021, without restrictions in terms of publication type and language. The Medical Subject Headings (MeSH) search terms and strategies were as follows: (IBS-D OR "Diarrhea predominant irritable bowel syndrome") AND (probiotics [MeSH] OR probiotics*) AND (random* OR controlled clinical trial* OR single blind* OR double blind* OR triple blind* OR RCT). The full search strategy is presented in the Supplementary material.

Inclusion and exclusion criteria

The RCTs, which evaluated the use of probiotics for IBS-D patients, were included in this study. The inclusion criteria were as follows: (a) the subjects were at least 18 years old and met the diagnostic criteria for IBS-D in the Roman criteria for functional gastroenteropathy and were not subjected to nationality, race, sex, etc. [39]; (b) the "intervention group" received any strain of probiotics or combination of probiotics at any dose, while the control group was treated with placebo; (c) the primary outcomes were IBS-D symptoms, abdominal pain, quality of life, and abdominal distension, and the secondary outcomes were stool frequency, satisfaction with bowel habits, flatulence, and adverse events. The exclusion criteria were as follows: (a) duplicate studies; (b) studies with insufficient data, such as protocols, animal experiments, conference proceedings, or abstracts; (c) pregnant or lactating mothers; and (d) the patients with gastrointestinal surgery.

Data extraction

Two researchers independently screened the literature and extracted the data. Any disagreement between them was resolved by consensus after discussion, or consultation with a third researcher. A pre-designed table was used to extract the data. The general data extracted from the studies were as follows: (a) basic characteristics, such as first author, publication year, study country, the sample size of the intervention and control groups, and duration of treatment; (b) general demographic characteristics, including age and gender; (c) T types and doses of probiotics; (d) primary and secondary outcomes as described in the inclusion criteria; and (e) risk of bias assessment.

Risk of bias assessment

The quality of the included studies was assessed using the risk of bias tool recommended by the Cochrane Handbook V.5.1.0 [40]. The assessment criteria included the following seven components: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases [41]. Each item was categorized as yes ("low risk of bias"), no ("high risk of bias"), or unclear ("moderate risk of bias"). When the risk of bias of all the seven components was low, the study was defined as overall "low risk of bias," while in case of high risk of bias for one or more bias components, the trial was defined as "high risk of bias." Under other conditions, the trial was defined as "unclear risk."

Certainty assessment

The quality of evidence, relating to the specific outcomes, was evaluated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system. The summary of findings was tabularized, including five factors: risk of bias, inconsistency, imprecision, indirectness, and publication bias [42]. The evidence certainty was classified as high, moderate, low, or very low [43].

Data synthesis and analysis

Meta-analysis was performed using RevMan 5.4 software. Statistical heterogeneity was analyzed for the included studies. The continuous data are generally presented as weighted mean differences (WMDs). However, in this study, the mean difference between the included studies was large; therefore, the standardized mean differences (SMDs) with 95% confidence intervals (CIs) were used. The dichotomous data were expressed as relative risks (RRs) with 95% CIs. The statistical heterogeneity was evaluated using the *I*-square (I^2) statistical test. In the case of significant heterogeneity($I^2 > 50\%$, $P < 0.05$), the random effect model was adopted, and a fixed effect model was used for the studies having non-significant heterogeneity [44, 45]. In addition, the subgroup analyses based on the species and strains of probiotics were also performed [32, 46]. The sensitivity analyses were performed using RevMan 5.4 to check the stability of the results and determine the specific effects of omitting an individual study on the results. Finally, funnel plots were used to assess publication bias when the number of the included studies for an outcome was more than 10 [47].

Results

Study selection

The detailed search and selection process for the collection of literature is presented in Fig. 1. A total of 1184 relevant records were initially identified, of which 226 records were excluded as duplicates. Eight hundred thirty-one records were excluded based on browsing titles and abstracts of the remaining 958 studies. Then, the full texts of the remaining 127 documents were read. Due to no relevant outcomes ($n = 28$), no IBS-D ($n = 66$), no full text ($n = 9$), and non-placebo ($n = 14$), 117 studies were excluded. Finally, a total of 10 RCTs were included in the meta-analysis [18, 19, 25, 30, 31, 48–52].

Study characteristics

This meta-analysis included the RCTs published between 2003 and 2021 with a total of 943 patients, including 483 in the intervention group and 460 in the control group. The sample sizes of included studies varied from 24 to 360 with the intervention duration ranging from 4 to 16 weeks. These studies were conducted in China (2/10), South Korea (2/10), the USA (2/10), Poland (2/10), Bangladesh (1/10), and Pakistan (1/10) (Table 1).

Risk of bias assessment

As shown in Fig. 2, in the random sequence generation analysis, one study used incorrect random sequence generation methods and was evaluated as "high risk of bias." Four studies were assessed as "high risk of bias" due to more than 10% of participants dropping out of these studies. In terms of other biases, seven trials were sponsored by commercial companies and were assessed as "high risk of bias."

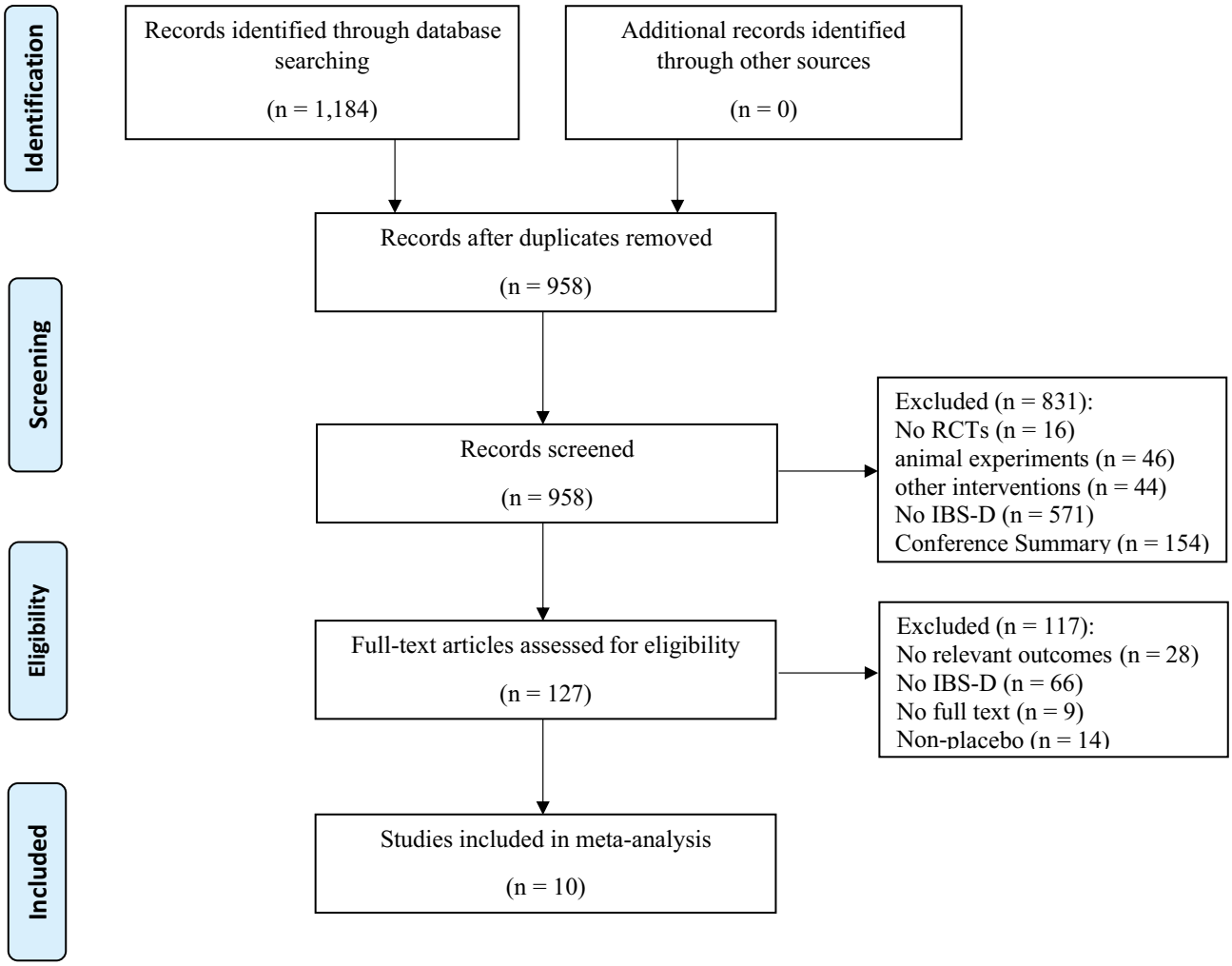

Fig. 1 Flow diagram of the literature screening process and results

Meta-analysis

Primary outcomes

IBS-D symptoms Eight RCTs, including 846 patients, reported the effectiveness of probiotics in improving the IBS-D symptoms in IBS-D patients [19, 25, 30, 31, 49–52]. The meta-analysis showed that probiotics therapy could significantly alleviate the overall symptoms of IBS-D patients as compared to the placebo group (SMD = −0.55, 95% CI: [−0.83, −0.27], $P < 0.05$). The subgroup analysis of the different strains and species indicated that both the individual species and their combination had statistically significant effects (single probiotics: SMD = −0.25, 95% CI: [−0.49, −0.01], $P < 0.05$; combination probiotics: SMD = −0.68, 95% CI: [−0.98, −0.42], $P < 0.05$). In addition, sensitivity analysis demonstrated that the results changed when Ishaque's study was omitted [53], suggesting the instability of this study (Fig. 3).

Abdominal pain Eight RCTs, including 829 patients, reported the effectiveness of probiotics therapy on abdominal pain in IBS-D patients [18, 25, 30, 31, 48, 49, 51, 52]. The meta-analysis showed that probiotics therapy could significantly reduce abdominal pain in IBS-D patients as compared to the placebo group (SMD = −0.43, 95% CI: [−0.57, −0.29], $P < 0.05$). The subgroup analysis of the different strains and species indicated that only combination probiotics had statistically significant effects. In addition, the sensitivity analysis, performed by omitting individual studies, showed no changes in the subgroups,

Table 1 The main characteristics of included studies

Study	Country	Simple (I/C)	Gender (M/F)	Age	Diagnostic criteria	Probiotics	Probiotic dosage	Duration of treatment	Outcomes
Ishaque et al. [49]	Bangladesh	181/179	I: 136/45 C: 145/34	I: 32.2 ± 10.1 C: 31.7 ± 9.7	Rome III	*Bacillus subtilis PXN 21*, *Bifidobacterium* spp., and *Lactobacillus* spp.	8×10^8 CFU	16 weeks	↓IBS-D symptoms ↑QoL
Choi et al. [52]	Korea	34/33	I: 18/17 C: 19/20	I: 43.0 ± 12.5 C: 40.6 ± 12.9	Rome II	*Saccharomyces boulardii*	Twice daily in capsules	4 weeks	↓IBS-D symptoms ↑QoL
Sun et al. [31]	China	105/95	I: 63/42 C: 53/42	I: 43.0 ± 12.5 C: 44.9 ± 13.0	Rome III	*Clostridium butyricum*	Thrice daily in capsules	4 weeks	↓IBS-D symptoms ↑QoL stool frequency
Kim et al. [48]	USA	12/13	I: 2/10 C: 5/8	I: 48 ± 19.75 C: 38 ± 12.26	Rome II	*VSL#3*	450 billion lyophilized bacteria/day	8 weeks	↓IBS-D symptoms ↓Abdominal bloating
Zeng et al. [30]	China	14/15	I: 10/4 C: 9/6	I: 44.6 ± 12.4 C:45.8 ± 9.2	Rome II	*Probiotic fermented milk* (*Streptococcus thermophilus*, *Lactobacillus bulgaricus*, *Lactobacillus acidophilus*, and *Bifidobacterium longum*)	Probiotic fermented milk 200 g or placebo drink 200 mL twice daily	4 weeks	↓IBS-D symptoms ↓Abdominal pain and flatulence
Abbas et al. [18]	Pakistan	37/35	I: 27/10 C: 26/9	I: 37 0.7 ± 11.6 C: 33.0 ± 12.0	Rome III	*Saccharomyces boulardii*	3×10^9 CFU	6 weeks	IBS-D symptoms ↑QoL
Michail et al. [51]	USA	15/9	I: 5/10 C: 3/6	21.8 ± 17	Rome III	*VSL#3*	9×10^{11} CFU	8 weeks	↓IBS-D symptoms ↓Abdominal pains QoL
Cha et al. [25]	Korea	25/25	I: 12/13 C: 14/11	I: 37.9 ± 12.4 C:40.3 ± 11.2	Rome III	*Multispecies probiotic mixture* (*Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Bifidobacterium breve*, *Bifidobacterium lactis*, *Bifidobacterium longum*, *Streptococcus thermophilus*)	1×10^9 CFU	8 weeks	↓IBS-D symptoms ↓Abdominal pains

Table 1 (continued)

Study	Country	Simple (I/C)	Gender (M/F)	Age	Diagnostic criteria	Probiotics	Probiotic dosage	Duration of treatment	Outcomes
Skrzydło-Radomańska et al. [19]	Poland	35/33	I: 10/25 C: 9/24	I: 43.2 ± 14.0 C: 36.7 ± 12.7	Rome III	*Lactobacillus* and *Bifidobacterium*	10 billion	8 weeks	↓IBS-D symptoms QoL
Skrzydło-Radomańska et al. [50]	Poland	25/23	I: 8/17 C: 9/14	I: 45.5 ± 11.1 C: 40.7 ± 14.4	Rome III	*Lactobacillus*, *Bifidobacterium* and *Streptococcus thermophilus*	*	8 weeks	↓IBS-D symptoms ↑QoL

I intervention group, *C* control group, *M* male, *F* female, *CFU* colony-forming units, *IBS-D* diarrhea irritable bowel syndrome, *QoL* quality of life

* not mentioned

indicating the stability of the results (SMD = −0.57, 95% CI: [−0.78, −0.41], $P < 0.05$) (Fig. 3).

Quality of life Seven RCTs, including 806 patients, reported the effectiveness of probiotics therapy for the quality of life in IBS-D patients [19, 25, 31, 49–52]. The meta-analysis showed that probiotics therapy could not significantly improve the quality of life in the IBS-D patients as compared to the placebo group (SMD = 0.31, 95% CI: [−0.26, 0.89], $P > 0.05$). The subgroup analysis of the different strains and species indicated that the use of only individual probiotics had statistically significant effects (SMD = 0.37, 95% CI: [0.13, 0.61], $P < 0.05$). In addition, the sensitivity analysis, performed by omitting individual studies, showed no change across subgroups, indicating that the results obtained were stable (Fig. 4).

Abdominal distension Eight RCTs, including 733 patients, reported the effectiveness of probiotics therapy on abdominal distension in IBS-D patients [18, 25, 30, 31, 48, 49, 51, 52]. The meta-analysis showed that probiotics therapy could significantly improve abdominal distension in IBS-D patients as compared to the placebo group (SMD = −0.45, 95%CI: [−0.81, −0.09], $P < 0.05$). The subgroup analysis of the different strains and species indicated that only the combination probiotics had statistically significant effects (SMD = −0.67, 95%CI: [−1.13, −0.21], $P < 0.05$). In addition, the sensitivity analysis, performed by omitting individual studies, showed no changes in the subgroups, indicating the stability of the results (Fig. 4).

Secondary outcomes

Stool frequency Two RCTs, including 97 patients, evaluated the effectiveness of probiotics therapy on stool frequency in IBS-D patients [18, 48]. The meta-analysis showed that probiotics therapy could not significantly improve stool frequency in the IBS-D patients as compared to the placebo group (SMD = 0.06, 95% CI: [−0.47, 0.59], $P > 0.05$). The sensitivity analysis was not performed due to the small number of studies (Fig. 5).

Satisfaction with bowel habits Two RCTs, including 605 patients, evaluated the effectiveness of probiotics therapy on the satisfaction with bowel habits in IBS-D patients [31, 49]. The meta-analysis showed that probiotics therapy could significantly improve satisfaction with bowel habits in IBS-D patients as compared to the placebo group (SMD = −0.63, 95% CI: [−1.14, 0.13], $P < 0.05$). The sensitivity analysis was not performed due to the small number of studies (Fig. 5).

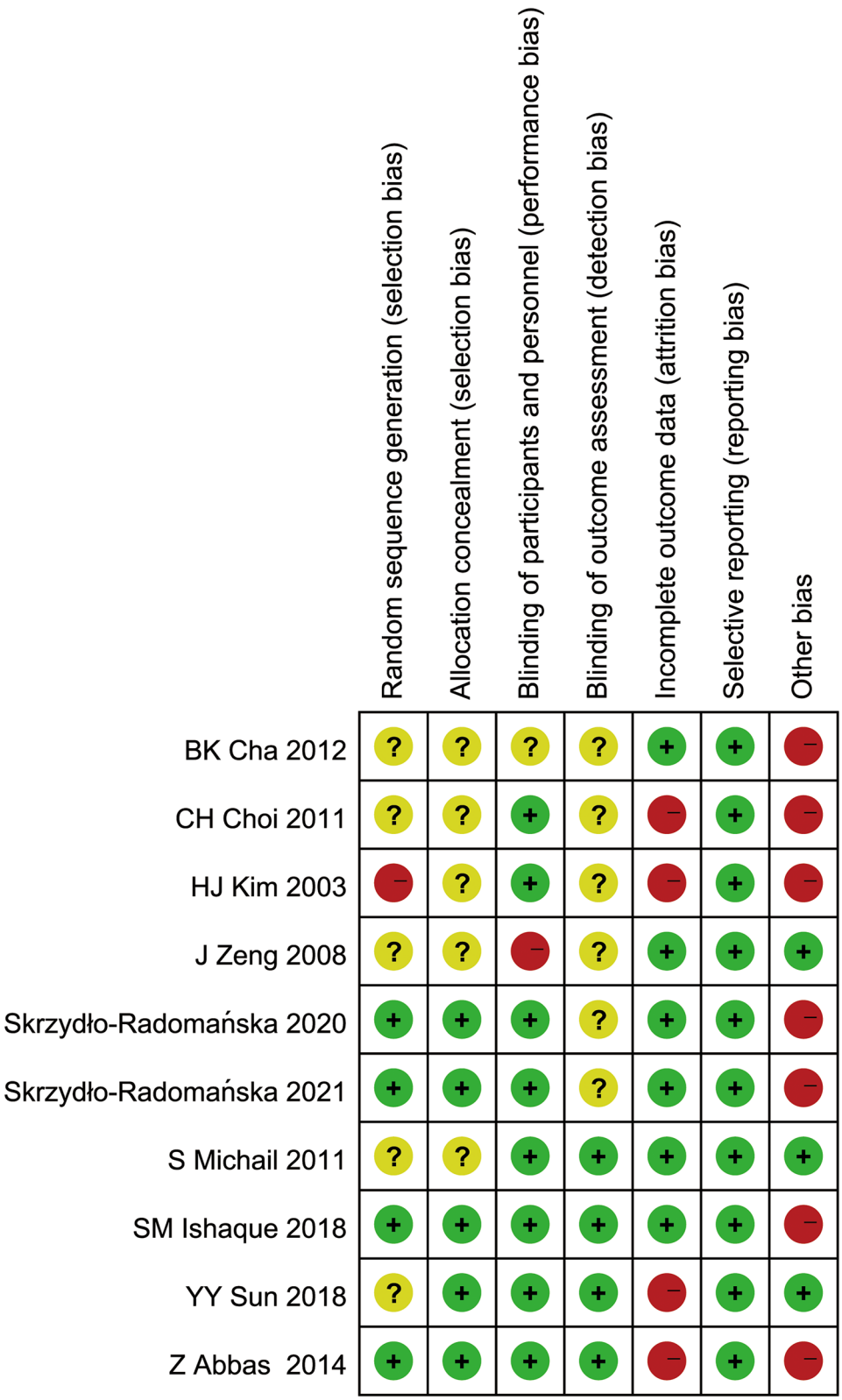

Fig. 2 Risk of bias assessment for the 10 studies included

Flatulence Four RCTs, including 170 patients, evaluated the effectiveness of probiotics therapy for flatulence in IBS-D patients [19, 30, 48, 50]. The meta-analysis showed that probiotics therapy could not significantly improve flatulence in the IBS-D patients as compared to the placebo group, and the difference was statistically insignificant (SMD = −0.19,

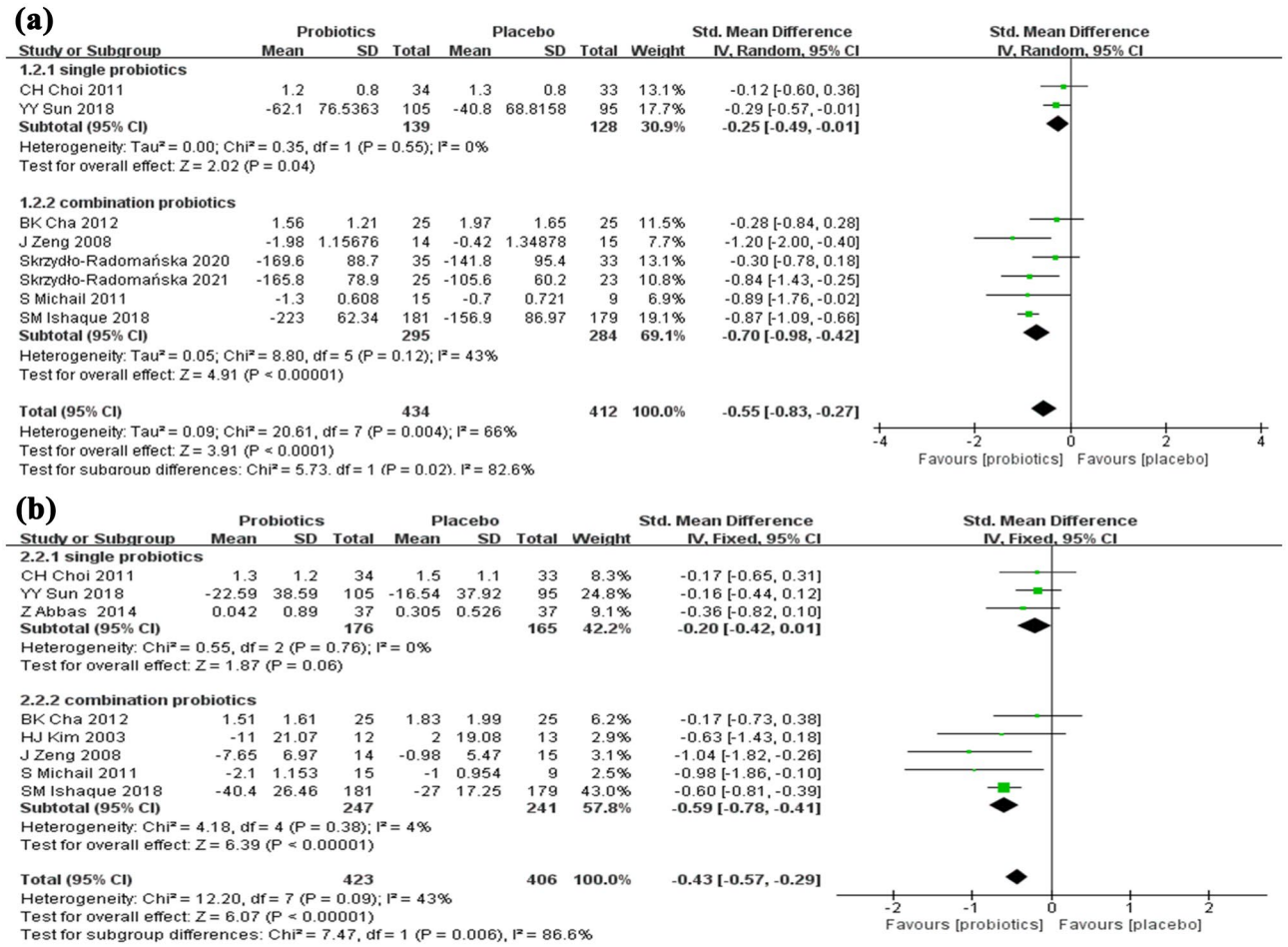

Fig. 3 Effect on IBS-D symptom (**a**) and abdominal pain (**b**) of IBS-D patients to probiotics: probiotic subgroups

95% CI: [−0.49, 0.11], $P > 0.05$) The sensitivity analysis was not performed due to the small number of studies (Fig. 5).

Adverse events Six RCTs, including 687 patients, reported the adverse events [18, 19, 25, 31, 50, 52]. Overall, 31 (10.6%) of the 293 patients in the probiotic group and 27 (9.2%) of the 294 patients in the placebo group experienced adverse events. The types and reporting of adverse events differed significantly across the different RCTs. Abdominal pain was reported as the most prevalent adverse event in four RCTs [18, 25, 31, 52]. There was no significant difference in the occurrence of adverse events in the probiotic group as compared to the placebo group (RR = 1.10, 95% CI = [0.72, 1.69], $P > 0.05$), and there was also homogeneity among the RCTs ($P > 0.05$) (Fig. 6).

Quality of evidence The summary of findings is listed in Table 2. The quality of evidence for each outcome ranged from very low (7/8) to low (1/8). The main reasons for the low quality (certainty) of evidence were the risk of bias (7/8), high heterogeneity among studies (inconsistency) (4/8), and wide confidence intervals (imprecision) (6/8).

Discussion

This meta-analysis showed that probiotics could effectively improve IBS-D in terms of improving the IBS-D symptoms, abdominal pain, abdominal distension, and satisfaction with bowel habits. This study suggested that the use of probiotics might be beneficial for IBS patients with diarrhea. Since there are different strains and species in probiotics, definitive conclusion for the selection of more effective strains and species was lacking. The subgroup analysis indicated that the combination of probiotics could more effectively improve the IBS-D symptoms and abdominal pain, while the use of individual probiotics could more effectively improve abdominal distension. Moreover, probiotics might have no

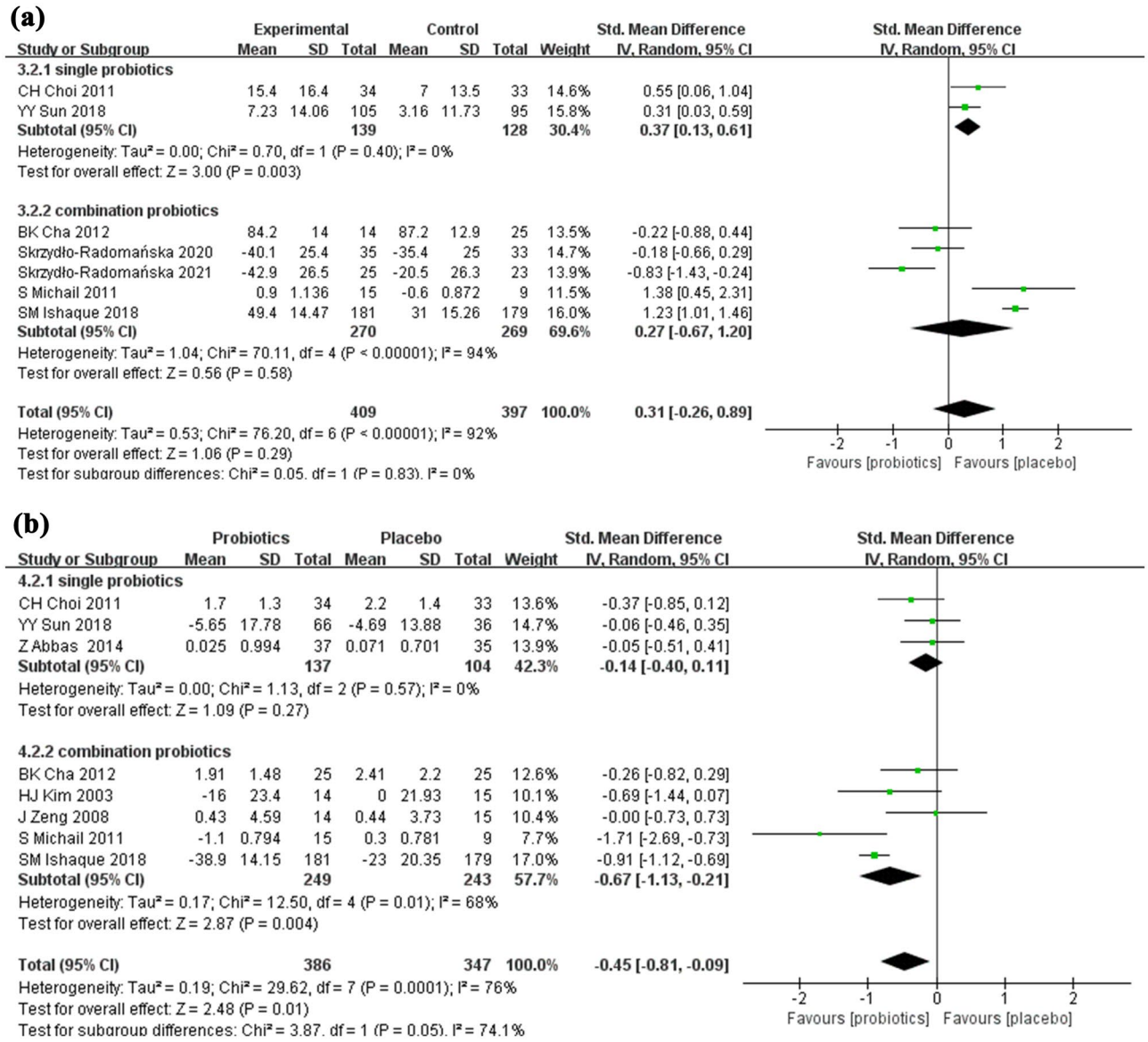

Fig. 4 Effect on the quality of life (**a**) and abdominal distension (**b**) of IBS-D patients to probiotics: probiotic subgroups

beneficial effects on the quality of life, stool frequency, and flatulence.

This study showed that combination probiotics could be more effective in improving the IBS-D symptoms and abdominal pain; this result was consistent with those of several previous studies [25, 36, 49]. Ishaque et al. indicated that the multi-strain combination probiotics could significantly improve symptoms and tolerance in IBS-D patients, and Cha et al. reported that the combination probiotics were effective in improving the overall IBS symptoms. A more recent review and meta-analysis by Sun et al. suggested that the specific combinations of probiotics or combinations of specific species and strains had beneficial effects on improving the general IBS symptoms and abdominal pain. Among the combination probiotics, *VSL#3* had beneficial effects in improving the IBS-D symptoms and abdominal pain. Ford et al. also showed that *VSL#3* could improve the global symptom scores or abdominal pain scores [32]. However, there was a lack of sufficient evidence, supporting these results, for specific species and strains of probiotics. Furthermore, the current study suggested that probiotics had no beneficial effect on the quality of life and stool frequency; this result differed from those of the previous studies [34, 54, 55]. These differences might be due to the differences in the study population, probiotic dose, dosage forms, and duration of treatment. The subgroup analysis

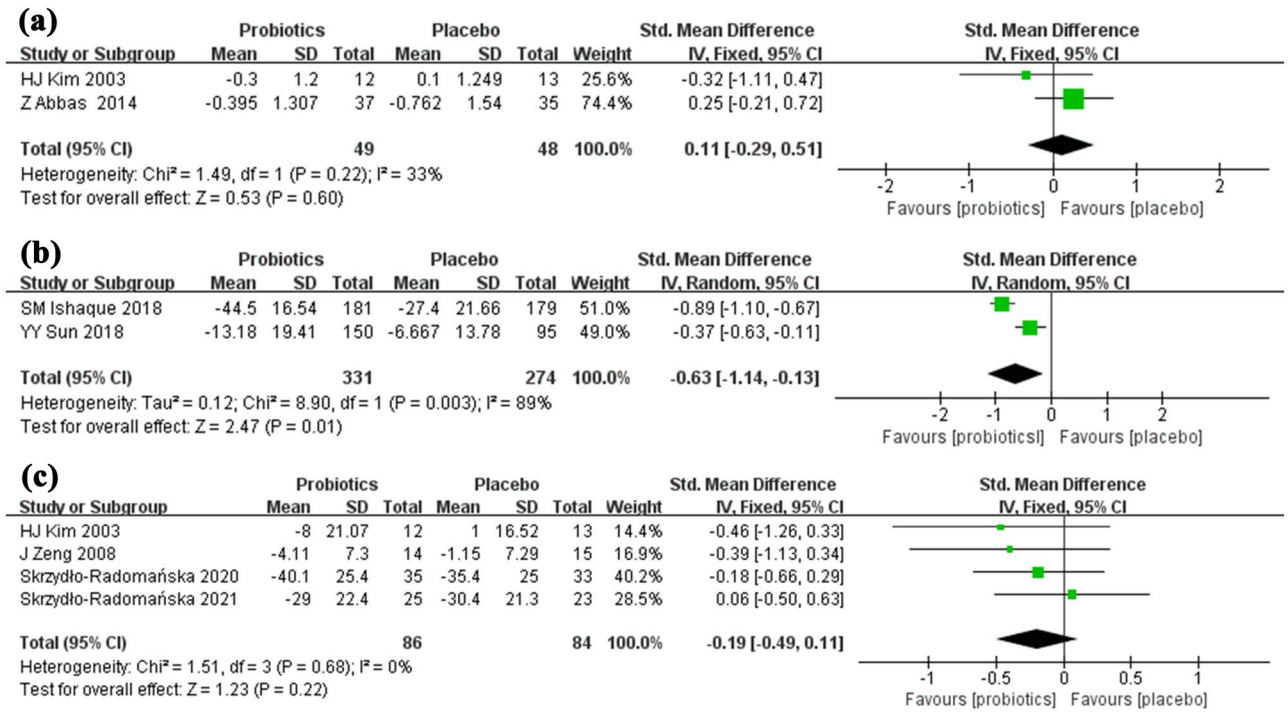

Fig. 5 Effect on stool frequency (**a**), satisfaction with bowel habits (**b**), and flatulence (**c**) of IBS-D patients to probiotics

indicated that the multi-strain probiotics containing *Bifidobacterium* could not significantly improve the quality of life of the IBS-D patients, which contradicted the findings of Asha et al. [56]. It was speculated that this might be caused by the large sample size of the one study included. However, the statistical significance did not change by the sensitivity analysis. Moreover, it was also speculated that due to the different effects of individual strains, studying all the species in combination might have obscured the specific efficacy of a species. Furthermore, the limited number of studies in the current systematic review might have caused the statistically insignificant differences.

In the current systematic review and meta-analysis, six studies reported adverse events, including abdominal pain, bloating, diarrhea, headache, nausea, vomiting, and skin rash [18, 19, 25, 31, 50, 52], which were generally tolerated. Besides, the probiotic and placebo groups showed no statistically significant differences in the occurrence of adverse events, suggesting the safety of probiotics for IBS-D patients. In order to explore the sources of heterogeneity, sensitivity analyses (IBS-D symptoms, quality of life, and abdominal distension) were performed. The results indicated that omitting one study could significantly reduce the heterogeneity in IBS-D symptoms [49]; the sample size and follow-up time might be the source of heterogeneity [49]. A study by Elfghi also suggested that the underpowered studies might be due to insufficient sample size [57]. For the quality of life and abdominal distension, omitting any study

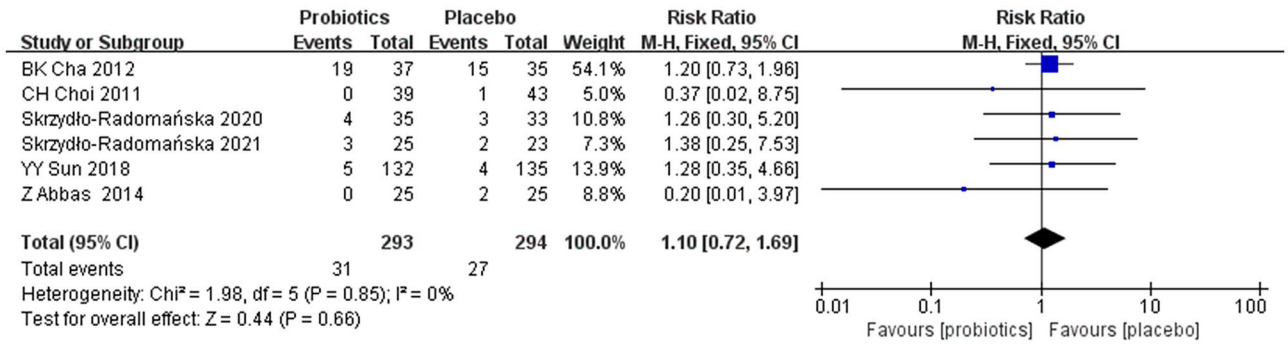

Fig. 6 Comparison between probiotics and placebo in terms of adverse events for IBS-D

Table 2 Summary of findings

Probiotics compared to placebo for IBS-D patients

Patient or population: IBS-D patients
Setting: -
Intervention: Probiotics
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with probiotics			
IBS-D symptoms	-	SMD 0.55 SD lower (0.83 lower to 0.27 lower)	-	846 (8 RCTs)	⨁◯◯◯[a] Very low
Abdominal pain	-	SMD 0.43 SD lower (0.57 lower to 0.29 lower)	-	829 (8 RCTs)	⨁◯◯◯[b] Very low
Quality of life	-	SMD 0.31 SD higher (0.26 lower to 0.89 higher)	-	806 (7 RCTs)	⨁◯◯◯[c] Very low
Abdominal distension	-	SMD 0.29 SD lower (1.43 lower to 0.84 higher)	-	733 (8 RCTs)	⨁◯◯◯[d] Very low
Stool frequency	-	SMD 0.06 SD higher (0.47 lower to 0.59 higher)	-	97 (2 RCTs)	⨁⨁◯◯[e] Low
Satisfaction with bowel habits	-	SMD 0.63 SD lower (1.14 lower to 0.13 lower)	-	605 (2 RCTs)	⨁◯◯◯[f] Very low
Flatulence	-	SMD 0.19 SD lower (0.49 lower to 0.11 higher)	-	170 (4 RCTs)	⨁◯◯◯[g] Very low
Adverse events	-	-	RR 1.10 (0.72 to 1.69)	587 (6 RCTs)	⨁◯◯◯[h] Very low

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

CI confidence interval, *SMD* standardized mean difference, *RCT* randomized controlled trial, *RR* risk ratio

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

[a]We downgraded the quality to very low due to the high risk of bias that existed in allocation concealment; high statistical heterogeneity between studies; and imprecision

[b]We downgraded the quality to very low due to the high risk of bias that existed in random sequence generation and allocation concealment; and imprecision

[c]We downgraded the quality of the evidence to very low due to the high risk of bias that existed in random sequence generation, allocation concealment, and blinding; high statistical heterogeneity between studies; and imprecision

[d]We downgraded the quality to very low due to the high risk of bias that existed in random sequence generation and blinding; and high statistical heterogeneity between studies

[e]We downgraded the quality to low due to the high risk of bias that existed in random sequence generation; and publication bias is more likely to exist

[f]We downgraded the quality to very low due to high statistical heterogeneity between studies and imprecision

[g]We downgraded the quality to very low due to the high risk of bias that existed in random sequence generation and blinding; and imprecision

[h]We downgraded the quality to very low due to the high risk of bias that existed in random sequence generation, allocation concealment, and blinding; and imprecision; and publication bias is more likely to exist

did not significantly alter the results, indicating the stability of the results.

Almost all the studies had a high risk of bias. Therefore, the results of this study should be referred to and discussed with caution. Most of the studies included in this meta-analysis implemented complete randomization, allocation concealment, and complete blinding of participants. However, one study had an inappropriate randomization method, and one

study did not have complete blinding of the participants; these high risks of bias might significantly reduce the reliability of the results [30, 48]. Therefore, rigorous training is necessary for researchers to clearly understand the significance of study quality and improve the reliability of RCTs according to the Cochrane quality assessment tool [58–60]. In addition, the importance of randomization and blinding of participants in RCTs is emphasized [61, 62].

Currently, no meta-analysis has specifically explored the effects of probiotics on IBS-D patients. A previous meta-analysis by Asha et al. included all the subtypes of patients and suggested that the impacts of probiotics on IBS-D patients were conflicting. Therefore, they recommended the inclusion of future RCTs, investigating the specific IBS subtypes. Although the IBS-D patients were included in this meta-analysis, the effects of probiotics on IBS-D were not discussed but only concluded that probiotics might improve the IBS symptoms. As compared to the previous studies, the current study only included adult patients with IBS-D and was the first systematic review and meta-analysis based on the RCTs of probiotics for IBS-D. Furthermore, this study tested the effectiveness of different strains and species of probiotics and evaluated the safety of probiotics in IBS-D using subgroup and sensitivity analyses.

This study had certain limitations. First, the poor quality of most included studies might affect the assessment of treatment outcomes. In order to improve the quality and authenticity of this meta-analysis, the Cochrane risk of bias tool was used to evaluate the quality of included studies, and the GRADE approach was used to evaluate the quality of evidence [63]. Moreover, this study strictly followed the PRISMA statement to improve the list of reporting items in this study. Besides, due to the small number of original studies, the subgroup analyses for the doses, duration of treatment, and regional differences of probiotics and funnel plot analysis were not performed. Therefore, there might be potential publication bias. Consequently, more RCTs with high quality, large sample sizes, and longer treatment duration and follow-up periods are required to further improve and update these results.

This study systematically reviewed the published RCTs, investigating probiotics therapy for IBS-D patients. However, due to the quantity and low quality of the RCTs, no definitive conclusion could be drawn. The results showed that probiotics therapy might have a beneficial effect on IBS-D patients, which might require the attention of clinicians. Probiotics therapy might be a very promising approach, especially in improving the IBS-D symptoms, abdominal pain, abdominal distension, and satisfaction with bowel habits. In addition, future RCTs should further evaluate the effects of multi-strain probiotic supplementation on the IBS-D symptoms in order to gain more insight into selection of effective strains and groups of IBS-D patients, who could potentially benefit most from the probiotics therapy.

Conclusion

With very low certainty evidence, probiotics therapy could effectively improve the IBS-D symptoms in the IBS-D patients as compared to the placebo group. Combination probiotics might be more effective in improving IBS-D symptoms, abdominal pain, abdominal distension, and satisfaction with bowel habits; however, their effects on quality of life, stool frequency, and flatulence remain unclear. Therefore, high-quality RCTs are needed to further validate the effectiveness of confirmed strains for the treatment of IBS-D. Future studies should focus more on the different aspects of probiotics.

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Declarations

Ethics approval and consent to participate Not applicable.

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