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Meta-analysis

Efficacy and safety of probiotics in irritable bowel syndrome: A systematic review and meta-analysis

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SUMMARY

Background: Irritable bowel syndrome (IBS) is a common gastrointestinal disease characterized by abdominal pain, distension, and altered bowel habits. Probiotics may alleviate IBS symptoms, but clinical trials remain conflicting.

Aims: To conduct a systematic review and meta-analysis of clinical trials to evaluate the efficacy and safety of probiotics for IBS patients.

Methods: We searched relevant trials in PubMed, Web of Science, Embase, Cochrane Library, and Google Scholar from 2000 to June 2023. Standardized mean difference (SMD) and 95% confidence interval (CI) were calculated for continuous outcomes. A risk ratio (RR) and a 95% CI were calculated for dichotomous outcomes.

Results: A total of 20 studies involving 3011 patients were obtained. The results demonstrated that probiotics are more effective than placebo in reducing global IBS symptoms improvement rate (RR = 1.401, 95% CI 1.182−1.662, P < 0.001) and quality of life scores (SMD = 0.286, 95% CI = 0.154−0.418, P < 0.001). Subgroup analyses showed that a shorter treatment time (less than eight weeks) could reduce distension scores (SMD = 0.197, 95% CI = 0.038−0.356, P = 0.015). High doses (daily dose of probiotics ≥ 10^{10}) or multiple strains of probiotics exhibit beneficial effects on abdominal pain (SMD = 0.412, 95% CI = 0.112−0.711, P = 0.007; SMD = 0.590, 95% CI = 0.050−1.129, P = 0.032; respectively). However, there was no significant benefit on global symptom scores (SMD = 0.387, 95% CI 0.122 to 0.653, P = 0.004) with statistically high inter-study heterogeneity (I2 = 91.9%, P < 0.001). Furthermore, there was no significant inter-group difference in terms of adverse events frequency (RR = 0.997, 95% CI 0.845−1.177, P = 0.973).

Conclusion: Probiotics are effective and safe for IBS patients. High doses or multiple probiotic strains seem preferable, but definite conclusions are challenging due to the high heterogeneity. Large-scale, well-designed, and rigorous trials are needed to confirm their effectiveness.

1. Introduction

Irritable bowel syndrome (IBS) is a highly prevalent functional gastrointestinal (GI) disease, with an 8.8% worldwide prevalence [1]. Globally, it is estimated that 4.1%−10% of adults are affected by IBS, with more than one-third of these cases attributed to IBS with constipation. It is characterized by recurrent abdominal pain and altered bowel habits, including diarrhea and/or constipation, without organic diseases [2]. IBS imposes substantial direct and indirect costs on the healthcare system, direct costs refer to healthcare-related expenses, while indirect costs refer to the costs associated with work absenteeism or work impairment. The total direct cost estimates per patient per year ranged from $348 to $8750, and indirect costs ranged from $355 to $3344 in the US [3]. According to Rome IV criteria, IBS is divided into subtypes based on bowel habit pattern: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), and unclassified IBS (IBS-U) [4]. The primary risk factors for IBS include female gender, a family history of IBS, and environmental factors like changes in diet, stress, or lifestyle [5,6]. Patients with IBS experience three troublesome symptoms: abdominal cramps, distension, and abdominal pain/discomfort [3]. These symptoms may lead to a decrease in quality of life (QOL) [7] and harm work and daily

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activities [8–10], resulting in a substantial economic healthcare burden.

The exact pathophysiology of IBS remains unclear [3]. It may involve chronic low-grade mucosal inflammation, GI motility and immune function alterations, visceral hypersensitivity increased intestinal permeability, and an imbalance of gut microbiota [11–14], and may be associated with changes in the brain-gut axis and psychological stress [15]. Current IBS treatments include antispasmodics, tricyclic antidepressants, selective serotonin reuptake inhibitors, and 5-hydroxytryptamine type-3 antagonists, which target and alleviate specific symptoms [16]. However, the evidence for the efficacy of most drug treatments for IBS is weak, leading to unsatisfactory symptom control or the possibility of adverse reactions in many patients.

Multiple studies have revealed that probiotics can theoretically modulate the gut microbiota, limit the colonization of pathogenic bacteria [17,18], and have moderate efficacy in improving IBS symptoms [19,20]. However, these results are limited due to the wide variety of studied strains and doses to date [21]. Therefore, this study aims to provide an updated and comprehensive systematic review and meta-analysis to assess the efficacy and safety of probiotics on global IBS symptom improvement rate, global symptom scores, individual symptom scores, and quality of life scores.

2. Methods

2.1. Search strategy and selection criteria

All procedures were performed according to the standards of Preferred Reporting Items for Systematic Reviews and Meta-Analyses [22]. We included all eligible randomized placebo-controlled trials (RCTs) of probiotics treatment for adult IBS patients published between 2000 and 2023in English-language peer-reviewed journals. A comprehensive literature search was conducted using PubMed, Web of Science, Embase, Cochrane Library, and Google Scholar. The search strategy was as follows: (“probiotics” [MESH Terms] OR “probiotics” [All Fields]) AND “irritable bowel syndrome” [MESH Terms] OR “irritable bowel syndrome” [All Fields] AND “randomized controlled trial”) OR “probiotics” [MESH Terms] AND “IBS-diarrhea” [All Fields] OR “probiotics” [MESH Terms] AND “IBS-constipation” [All Fields] OR “probiotics” [MESH Terms] AND “IBS-mixed” [All Fields])

2.2. Data extraction

A manual search of possible references of interest was carried out. The studies conformed to the following criteria were considered: (1) the studies were randomized controlled trials (RCTs) comparing probiotics with placebo; (2) diagnostic criteria included any version of the Rome criteria; (3) the participants were $\geq$ 18 years old; (4) minimum treatment duration was seven days. (4) minimum sample size was 30 patients. Exclusion criteria included: (1) studies with insufficient information; (2) probiotics in combination with other drugs; (3) the control group was not placebo; (4) data were unavailable after contacting the authors; (5) early phase one or two safety or mechanism of action studies, narrative reviews, case reports, conference proceedings, retrospective studies, and systematic reviews. The protocol was registered with Prospero (Prospero #: CRD42023427120).

Initial study screening and data extraction were independently performed by one researcher, then reviewed by one of the other two researchers according to the PRISMA 2020 guidelines [23]. Any divergence was discussed until reaching a consensus. Previously published duplicate studies were eliminated. For trials with ambiguous data, attempts were made to contact authors for additional information. The following data was extracted: Author and year of study, country, duration of therapy, sample size (number of males/females), age, IBS diagnostic criteria, strain or type of intervention, and probiotic dosage.

2.3. Outcomes assessment

Due to the lack of consensus on a standardized evaluation of the efficacy of irritable bowel syndrome, we used the most common indicators in these trials to assess the improvement in IBS.

The primary outcomes of the meta-analysis were: (1) Global IBS symptom improvement: this included global symptom improvement rate, which is a dichotomous outcome defining the number of patients who reported improvement in their overall IBS symptoms at the end of the study and global symptom scores which is a continuous outcome comparing the change of overall IBS symptom scores from baseline to end of study; (2) Predominant symptoms improvement: this focused on continuous variables especially measuring the change in abdominal pain, distension and urgency scores from baseline to end of intervention; (3) Quality of life (QOL): this involves continuous variables, standard indicators of QOL include wealth, employment, the environment, physical and mental health, education, recreation and leisure time, social belonging, religious beliefs, safety, security, and freedom. The SF-36, a generic well-validated tool for measuring HRQOL, was used here to assess the change in total QOL scores from baseline to end of intervention referred to a published study [7]. To evaluate the safety of probiotics, the secondary outcome was the number of adverse reactions reported by study participants.

2.4. Assessment of study quality and risk of bias

Two reviewers independently reviewed and scored each included RCT, and any disagreement was resolved through discussion. The risk of bias was assessed using the Cochrane Handbook [24]. The risk of bias was assessed and graded as high, low, or not reported for each of the six bias areas: selection bias (random sequence generation and allocation concealment), performance bias (blinding participants and evaluators), detection bias (blinding outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting) and other issues (eligibility criteria, baseline and conflicts of interests).

2.5. Data synthesis and statistical methods

The outcomes were illustrated graphically using Review Manager version 5.3.5 (the Nordic Cochrane Center, Copenhagen, Denmark). The funnel plots were calculated by Stata Statistical Software: Release 14 (Stata Corp LP; College Station, TX). In terms of statistical analysis, continuous variables were presented as standardized mean difference (SMD), whereas dichotomous data were evaluated by relative risk (RR), with 95% confidence intervals (CIs). A subgroup analysis was conducted based on the treatment type, daily doses of probiotics, and duration of therapy. Interstudy heterogeneity was evaluated using the I^2 statistic, and a random effect model was applied when significant heterogeneity was present ($I^2 \geq 50\%$). Sensitivity analyses were conducted to explore possible explanations when significant heterogeneity was observed. The publication bias was evaluated using a funnel plot, Begg's, and Egger's tests. A P value less than 0.05 was considered statistically significant.

3. Result

3.1. Search results

Using our search criteria, a comprehensive electronic database search yielded a total of 2383 articles. In the phases of evaluating duplicate studies and reviewing the titles and abstracts of the articles, 1762 and 446 studies were excluded, respectively. The full text of the remaining 175 articles was screened for retrieval, among these, 22 were excluded due to the failure retrieval. Then the 153 studies were considered as eligibility, after careful reviewing, 21 papers (not a controlled clinical trial), 17 papers (not an empirical study), 19 papers (sample size < 40), 15 papers (probiotics were not the only active components of the treatment condition), 8 papers (unclear or ineligible diagnostic criteria) and 36 papers (lack of desired information) were excluded. Finally, 37 unique studies were included in the meta-analysis. The detailed flowchart of the selection procedure was shown in Fig. 1.

3.2. Characteristics of included studies

In 37 RCTs [25–61], 2675 participants were assigned to the intervention group and 2499 to the control group, with 32.51% male and 67.49% female. The sample sizes ranged from 36 to 456, with the study population predominantly mixed IBS subtypes (85%) diagnosed with Rome II/III criteria (81%). The duration of the intervention varied from 4 to 24 weeks. Table 1 presents the characteristics of the studies included in the present systematic review and meta-analysis.

3.3. Risk of bias

The risk of bias is shown in Figs. 2 and 3. Sixteen studies describe the sequence generation process in detail, whereas seventeen studies did not describe whether adequate concealment of allocation procedure was used, resulting in an uncertain risk of selection bias. All included trials reported participant blinding methods. Most of the other domains of study bias (performance, detection, attrition, reporting) were rated as having low bias. Overall, the risk of bias for each included study ranged from low to uncertain.

3.4. Sensitivity analysis

The influence of a single study on the overall meta-analysis estimate was examined by removing one study at a time, and the result revealed no significant difference (Figure S1), indicating statistically reliable results.

3.5. Efficacy of probiotics on global IBS symptom improvement

3.5.1. Efficacy of probiotics on global symptom improvement rate

Twenty RCTs involving 3011 patients reported the efficacy of probiotics on the global IBS symptom improvement rate. Among these, 749 (48.4%) of 1549 patients in the probiotic group experienced an improvement in IBS symptoms after treatment compared to 509 (34.8%) of 1462 placebo patients. The results revealed that probiotics significantly increased global IBS symptoms improvement rate compared to placebo by the end of the study (RR = 1.401, 95% CI 1.182–1.662, P < 0.001), with statistically significant inter-study heterogeneity (I^2 = 71.7%, P < 0.001, Fig. 4). Additionally, subgroup analysis based on the duration of therapy and treatment type led to the loss of inter-study heterogeneity for intervention durations longer than eight weeks (I2 = 0.0%, P = 0.766) and probiotic combination interventions (I^2 = 30.7%, P = 0.163), respectively (Figure S2). There was no evidence of publication bias based on the absence of significant asymmetry in the funnel plot (Begg's test, P = 0.538; Egger's test, P = 0.152; Figure S3).

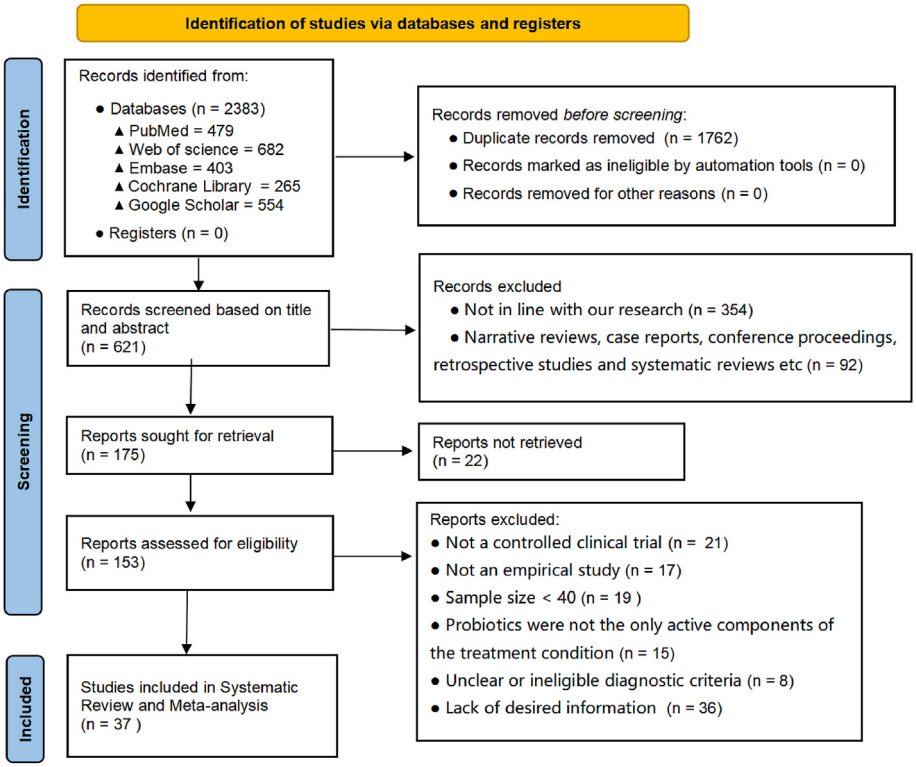

Fig. 1. Flow diagram of the study selection process.

Table 1
Characteristics of randomized controlled trials of probiotics versus placebo in irritable bowel syndrome.

Author and year of study	Country	Duration	Sample size (male/female)	Age [years], mean ± SD	Diagnostic criteria	Intervention	Strain or type of intervention	Probiotic dosage
Abbas et al. (2014)	Pakistan	6 weeks	I:27/10 P:26/9	I:37.7 ± 11.6 P:3.0 ± 12.0	Rome III, IBS-D	single-strain	S.boulardii	0ne capsule (750 mg) containing S.boulardii (3 × 10^9 CFU/capsule) o.d
Amirimani et al. (2013)	Iran	4 weeks	I:21/32 P:15/24	I:44.9 ± 13.0 P:37.7 ± 10.5	Rome III, All	single-strain	L.reuteri	One tablet containing L.reuteri (1 × 10^8 live cells/tablet) o.d
Begtrup et al. (2013)	Denmark	6 months	I:16/51 P:18/46	I:31.6 ± 10.1 P:29.4 ± 8.6	Rome III, All	Combination, 3 strain mix	L.paracasei ssp paracasei F19,L.acidophilus La5 and B.lactis Bb12	Four capsules containing L.paracasei ssp paracasei F19,L.acidophilus La5 and B.lactis Bb12 (1.3 × 10^10 CFU/capsule) o.d
Charbonneau et al. (2013)	Ireland	8 weeks	I:8/31 P:6/31	I:47.0 ± 1.96 P:43.2 ± 2.01	Rome II, All	single-strain	B.infantis 35,624	one capsule containing B.infantis 35,624 (1 × 10^9 CFU/capsule)o.d
Choi et al. (2011)	Korea	4 weeks	I:18/17 P:19/20	I:40.2 ± 13.1 P:40.6 ± 12.9	Rome II, IBS-D and IBS-M	single-strain	S.boulardii	Two capsules containing S.boulardii (2 × 10^11 live cells/capsule) b.i.d
Dapoigny et al. (2012)	France	4 weeks	I:10/15 P:5/20	I:46.1 ± 11.3 P:48.0 ± 10.8	Rome III, All	single-strain	L.casei variety rhamnosus	Three capsules containing L.casei variety rhamnosus (2 × 10^8 CFU/capsule)o.d
Ducrotté et al. (2012)	France	4 weeks	I:70/38 P:81/25	I:36.5 ± 12.1 P:38.4 ± 13.1	Rome III, All	single-strain	L.plantarum 299v (DSM 9843)	one capsule containing L.plantarum (DSM 9843) (1 × 10^10 CFU/capsule)o.d
Guglielmetti et al. (2011)	Italy	4 weeks	I:19/41 P:21/41	I:36.7 ± 12.4 P:40.9 ± 12.8	Rome III, All	single-strain	B.infantis MIMBb75	one capsule containing B.infantis MIMBb75 (1 × 10^9 CFU/capsule)o.d
Gupta et al. (2021)	India	80 days	I:13/7 P:15/5	I:36.20 ± 9.81 P:34.80 ± 11.06	Rome IV, All	single-strain	B.coagulans	A powder form containing B.coagulans (2 × 10^9 CFU/ml) t.i.d
Guyonnet et al. (2007)	France	6 weeks	I:29/106 P:39/93	I:49.4 ± 11.4 P:49.2 ± 11.4	Rome II, IBS-C	Combination, 3 strain mix	B.animalis, S.thermophilus and L.delbrueckii	A fermented milk drink containing B.animalis (1.25 × 10^10 CFU/pot),S.thermophilus and L.delbrueckii (1.2 × 10^9 CFU/pot) b.i.d
Hod et al. (2017)	Israel	8 weeks	I:0/54 P:0/53	I:29.0 ± 4.0 P:30.0 ± 6.0	Rome III, IBS-D	Combination, 11 strain mix	L.rhamnosus, L.paracasei, L.plantarum, L.acidophilus, L.bulgaricus, L.lactis, B.bifidum, B.longum, B.breve, B.infantis and S.thermophilus	One capsule containing 11 different strains (2.5 × 10^10 CFU/capsule) b.i.d.
Hong et al. (2009)	Korea	8 weeks	I:25/11 P:22/12	I:36.0 ± 2.0 P:38.0 ± 3.0	Rome III, All	Combination, 4 strain mix	*B. bifidum*, B.lactis, L.acidophilus and L.casei	A powder form containing 4 different strains (4 × 10^10 CFU/ml) b.i.d
Jafari et al. (2014)	Iran	4 weeks	I:21/33 P:22/32	I:36.6 ± 12.1 P:36.8 ± 11.0	Rome III, All	Combination, 4 strain mix	B.animalis, L.acidophilus, L.delbrueckii and S.thermophilus	One capsule containing 4 different strains (4 × 10^9 CFU/capsule) b.i.d.
Kajander et al. (2008)	Finland	20 weeks	I:2/41 P:4/39	I:50.0 ± 13.0 P:46.0 ± 13.0	Rome II, All	Combination, 4 strain mix	LGG, L.rhamnosus,B.breve and P.freudenreichii ssp	One capsule containing 4 different strains (8–9*10^9 CFU/capsule) o.d.
Khodadoostan et al. (2018)	Iran	6 months	I:21/12 P:22/12	I:32.97 ± 10.79 P:35.15 ± 11.20	Rome III, IBS-D	Combination, 7 strain mix	L.casei, L.acidophilus, L.rhamnosus, L.bulgaricus, B.breve, B.longum, and S.thermophilus	Two capsules containing 7 different strains (1 × 10^9 CFU/capsule) o.d.
Kruis et al. (2012)	Germany	12 weeks	I:12/48 P:16/44	I:46.3 ± 12.1 P:45.1 ± 12.7	Rome II, All	single-strain	E.coli Nissle 1917	One capsule containing E.coli Nissle 1917 (2.5–25 × 10^9 CFU/capsule) o.d.for 4 days then b.i.d.for 12 weeks
Lewis et al. (2020)	Canada	8 weeks	I:22/64 P:17/64	I:42.42 ± 12.30 P:41.84 ± 16.14	Rome III, All	single-strain	B.longum	one capsule containing B.longum (1 × 10^10 CFU/capsule)o.d
Lewis et al. (2020)	Canada	8 weeks	I:17/67 P:17/64	I:42.31 ± 16.88 P:41.84 ± 16.14	Rome III, All	single-strain	L.paracasei	one capsule containing L.paracasei (1 × 10^10 CFU/capsule)o.d
Lyra et al. (2016)	Finland	12 weeks	I:37/94 P:35/94	I:47.2 ± 12.5 P:49.4 ± 12.9	Rome III, All	single-strain	L.acidophilus NCFM	one capsule containing L.acidophilus NCFM (1 × 10^9 CFU/capsule)o.d
Majeed et al. (2016)	India	90 days	I:7/11 P:10/8	I:36.2 ± 11.07 P:35.4 ± 10.75	Rome III, IBS-D	single-strain	*Bacillus coagulans* MTCC 5856	One tablet containing *Bacillus coagulans* MTCC 5856 (2 × 10^9 CFU/tablet) o.d
Martoni et al. (2020)	India	6 weeks	I:53/58 P:55/54	I:39.41 ± 11.80 P:37.6 ± 10.1	Rome IV, All	single-strain	L.acidophilus	

(*continued on next page*)

Table 1 (*continued*)

Author and year of study	Country	Duration	Sample size (male/female)	Age [years], mean ± SD	Diagnostic criteria	Intervention	Strain or type of intervention	Probiotic dosage
								one capsule containing L.acidophilus (1×10^{10} CFU/capsule)o.d
Martoni et al. (2020)	India	6 weeks	I:59/51 P:55/54	I:41.6 ± 11.1 P:37.6 ± 10.1	Rome IV, All	single-strain	B.lactis	one capsule containing B.lactis (1×10^{10} CFU/capsule)o.d
Mourey et al. (2022)	France	8 weeks	I:28/202 P:36/190	I:41.2 ± 13.96 P:39.9 ± 14.56	Rome IV, All	single-strain	S.cerevisiae	Two capsules containing *S. cerevisiae* (8×10^{9} CFU/capsule) o.d.
Niv et al. (2005)	Israel	6 months	I:7/20 P:11/16	I:45.7 ± 14.2 P:45.6 ± 16.1	Rome II, All	single-strain	L.reuteri ATCC 55730	Four tablets containing L.reuteri ATCC 55730 (1×10^{8} CFU/tablet) o.d.for 7 days then two tablets o.d.until the end of the study
Pineton de Chambrun et al. (2015)	France	8 weeks	I:14/72 P:11/82	I:42.5 ± 12.5 P:45.4 ± 14	Rome III, All	single-strain	S.cerevisiae CNCM I-3856	one capsule containing S.cerevisiae CNCM I-3856 (4×10^{9} CFU/capsule)o.d
Preston et al. (2018)	USA	12 weeks	I:29/47 P:16/21	I:40.6 ± 13.4 P:39.9 ± 14.0	Rome III, All	Combination, 3 strain mix	L.acidophilus CL1285, L.casei LBC80R and L.rhamnosus CLR2	Two capsules containing 3 different strains (5×10^{10} CFU/capsule) o.d.
Roberts et al. (2013)	UK	4 weeks	I:15/73 P:15/76	I:44.7 ± 11.9 P:43.7 ± 12.8	Rome III, All	Combination, 3 strain mix	B.lactis, S.thermophilus and L.bulgaricus.	A fermented milk drink containing B. lactis (1.25×10^{10} CFU/ cup),*S. thermophilus* and *L. bulgaricus* (1.2×10^{9} CFU/cup) b.i.d
Sadrin et al. (2020)	France	8 weeks	I:11/29 P:12/28	I:48.9 ± 8.4 P:48.9 ± 8.0	Rome III, All	Combination, 2 strain mix	L.acidophilus NCFM and L.acidophilus subsp.helveticus	Two capsules containing 2 different strains (5×10^{9} CFU/capsule) o.d.
Shavakhi et al. (2014)	Iran	2 weeks	I:46/20 P:39/24	I:36.1 ± 7.9 P:36.4 ± 10.5	Rome II, All	Combination, 7 strain mix	L.casei, L.rhamnosus, L.acidophilus, L.delbrueckii ssp. bulgaricus, B.breve, B.longum, S.thermophilus and FOO	One capsule containing 7 different strains (1×10^{8} CFU/capsule) b.i.d.
Simrén et al. (2010)	Sweden	8 weeks	I:11/26 P:11/26	I:42.0 ± 15.0 P:44.0 ± 16.0	Rome II, All	Combination, 3 strain mix	L.paracasei, L.acidophilus and B.lactis	A fermented milk drink containing 3 different strains (1×10^{10} CFU/pot) b.i.d
Sinn et al. (2008)	Korea	4 weeks	I:6/14 P:8/12	I:41.9 ± 14.4 P:47.5 ± 11.0	Rome III, IBS-D and IBS-C	single-strain	L.acidophilus SDC 2012 and 2013	One capsule containing L.acidophilus SDC 2012 and 2013 (2×10^{9} CFU/ml) b.i.d.
Sisson et al. (2014)	UK	12 weeks	I:40/84 P:17/45	I:39.6 ± 10.5 P:36.8 ± 10.8	Rome III, All	Combination, 4 strain mix	L.rhamnosus, L.plantarum, L.acidophilus and *Enterococcus faecium*	A drink (1 ml/kg) containing 4 different strains (2×10^{8} CFU/ml)o.d
Skrzydło-Radomańska et al. (2021)	Poland	8 weeks	I:8/17 P:9/14	I:45.5 ± 11.1 P:40.7 ± 14.4	Rome III, IBS-D	Combination, 10 strain mix	four Bifi-dobacterium, five Lactobacillus, and one *Streptococcus thermophilus*	One capsule containing 10 different strains (2.5×10^{9} CFU/capsule) b.i.d
Spiller et al. (2016)	UK	12 weeks	I:31/161 P:31/156	I:45.3 ± 15.7 P:45.4 ± 14.1	Rome III, All	single-strain	S.cerevisiae CNCM I-3856	Two capsule containing S.cerevisiae CNCM I-3856 (4×10^{9} CFU/capsule)o.d
Stevenson et al. (2014)	South Africa	8 weeks	I:2/52 P:0/27	I:48.1 ± 13.5 P:47.3 ± 12.1	Rome II, All	single-strain	L.plantarum 299v	Two capsules containing L.plantarum 299v (5×10^{9} CFU/capsule) o.d
Sun et al. (2018)	China	4 weeks	I:63/42 P:53/42	I:43.0 ± 12.5 P:44.9 ± 13.0	Rome III, IBS-D	single-strain	*Clostridium butyricum*	Three capsules containing *Clostridium butyricum* (6.3×10^{6} CFU/capsules) t.i.d
Thijssen et al. (2016)	Netherlands	8 weeks	I:13/26 P:12/29	I:41.1 ± 14.8 P:42.4 ± 13.5	Rome II, All	single-strain	L.casei Shirota (LcS)	A fermented milk drink containing LcS (6.5×10^{9} CFU/bottle) b.i.d
Williams et al. (2009)	UK	8 weeks	I:3/25 P:4/20	I:40.0 ± 12.0 P:38.0 ± 11.0	Rome II, All	Combination, 4 strain mix	L.acidophilus CUL-60, L.acidophilus CUL-21, B.lactis and B.bifidum	One capsule containing 4 different strains (2.5×10^{10} CFU/capsule) o.d.
Yoon et al. (2015)	Korea	4 weeks	I:19/20 P:24/18	I:59.9 ± 11.1 P:58.8 ± 13.3	Rome III, All	Combination, 6 strain mix	B.bifidum, B.lactis, B.longum, L.acidophilus, L.rhamnosus and S.thermophilus	Two capsules containing 6 different strains (5×10^{9} CFU/capsule) o.d.

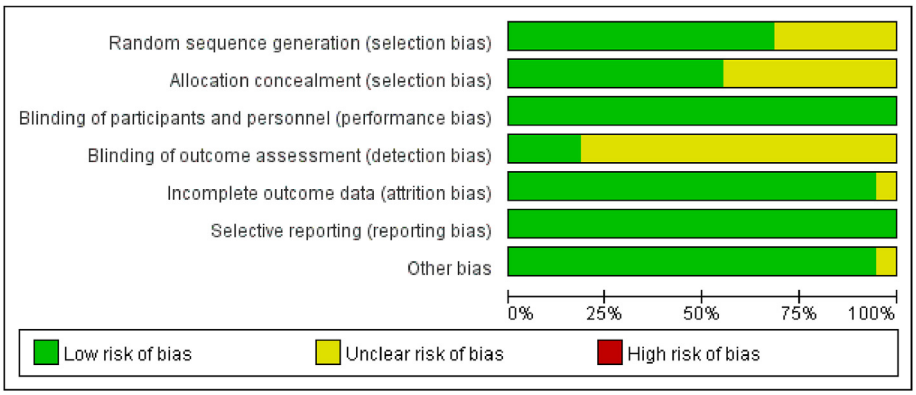

Fig. 2. Risk of bias.

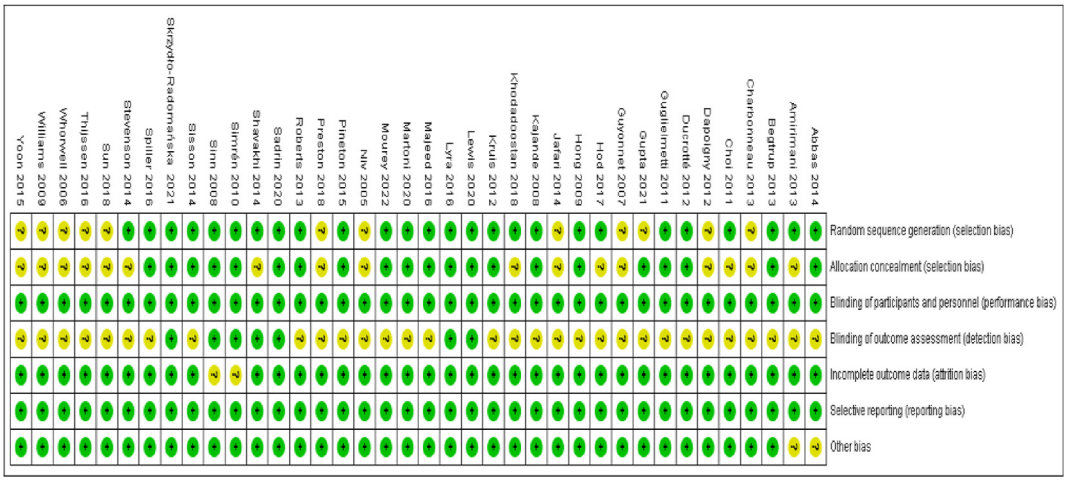

Fig. 3. Risk of bias summary.

3.5.2. *Efficacy of probiotics on global symptom scores*

A total of 18 RCTs, including 22 comparisons with 2720 patients, reported the efficacy of probiotics on global symptom scores, with two trials examining two different treatment type groups and one examining three different IBS sub-type groups. Figure 5 demonstrates that probiotics had no statistically significant effect on improving the global IBS symptoms compared to placebo (SMD = 0.387, 95% CI 0.122 to 0.653, P = 0.004; with statistically significant inter-study heterogeneity (I^2 = 91.9%, P < 0.001). Due to heterogeneity, a subgroup analysis was conducted to identify possible sources. Subgroup analysis by treatment type, probiotics daily doses, and treatment duration revealed the same outcome and did not explain inter-study heterogeneity (Figure S4). There was no significant asymmetry in the funnel plot (Begg's test, P = 0.573; Egger's test, P = 0.231; Figure S3), indicating no evidence of publication bias.

3.6. *Efficacy of probiotics on predominant symptom scores*

3.6.1. *Efficacy of probiotics on abdominal pain scores*

A total of 23 RCTs, including 26 comparisons with 3078 patients, reported the probiotics' efficacy on abdominal pain scores, with one trial examining two different treatment type groups and one examining three different IBS sub-type groups. The results showed that probiotics significantly increased abdominal pain scores compared to placebo by the end of the study (SMD = 0.387, 95% CI 0.122 to 0.653, P = 0.004; Figure S5), with statistically significant inter-study heterogeneity (I^2 = 91.9%, P < 0.001). There was no significant asymmetry in the funnel plot (Begg's test, P = 0.537; Egger's test, P = 0.475; Figure S3), indicating no evidence of publication bias.

A subgroup analysis based on the treatment type revealed that combination probiotics significantly reduced abdominal pain scores (SMD = 0.412, 95% CI = 0.112–0.711, P = 0.007), and no statistical difference was observed between single-strain probiotics and placebo groups (SMD = 0.395, 95% CI = −0.021–0.810, P = 0.063; Fig. 6). Subgroup analysis based on probiotics' daily dose demonstrated that high doses of probiotics (daily dose of probiotics ≥ 10^10) significantly reduced abdominal pain scores (SMD = 0.590, 95% CI = 0.050–1.129, P = 0.032), and there was no statistical difference between low doses probiotics (daily dose of probiotics < 10^10) and placebo groups (SMD = 0.276, 95% CI = −0.015–0.566, P = 0.063; Fig. 6). The significant effect of probiotics on abdominal pain scores remained significant in subgroup analyses based on the duration of therapy. Subgroup analysis by the treatment type, daily doses of probiotics, and duration of therapy did not explain the inter-study heterogeneity (I^2 > 84%, P < 0.001; Fig. 6).

3.6.2. *Efficacy of probiotics on distension scores*

A total of 18 RCTs, including 21 comparisons with 2672 patients, reported the efficacy of probiotics on distension scores, with one trial examining two different treatment types and another examining three different IBS subtypes. The results indicated that probiotics had no statistically significant effect on

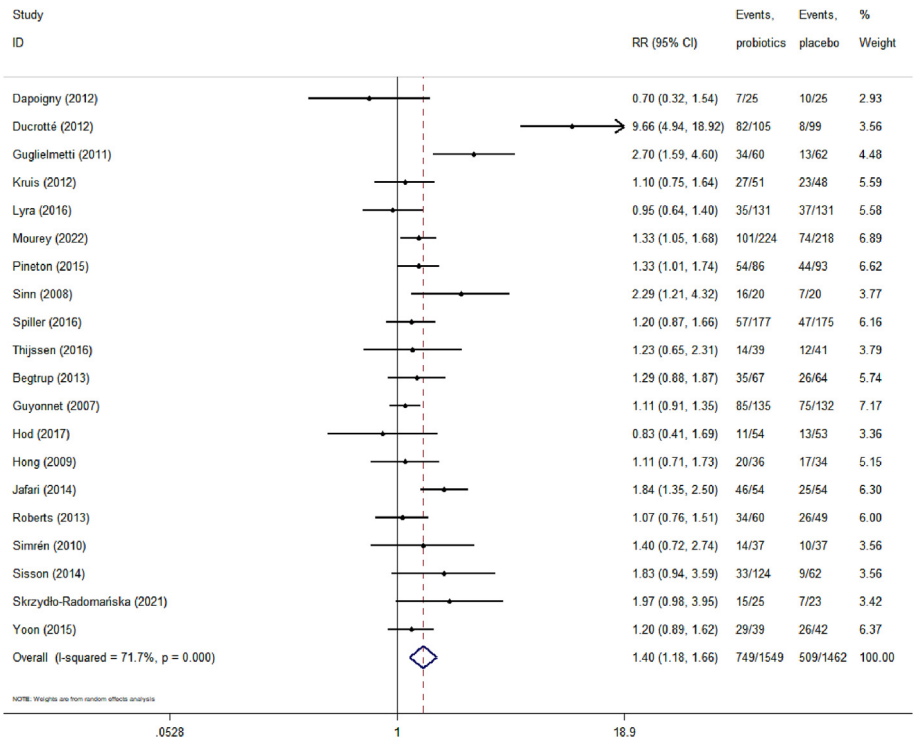

Fig. 4. Forest plot of efficacy on global symptom improvement rate.

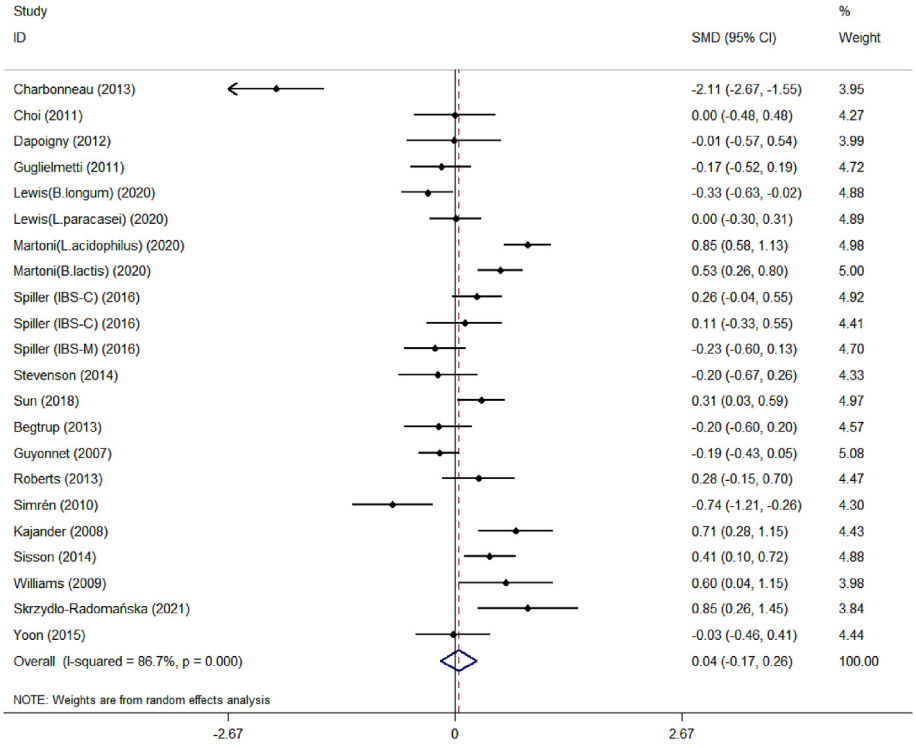

Fig. 5. Forest plot of efficacy on global symptom scores.

improving abdominal pain scores compared to placebo (SMD = 0.112; 95% CI -0.008 to 0.231; P = 0.066; Figure S6), with statistically significant inter-study heterogeneity (I^2 = 55.6%, P = 0.001). There was no significant asymmetry in the funnel plot (Begg's test, P = 1.000; Egger's test, P = 0.959; Figure S3), indicating no evidence of publication bias.

A subgroup analysis based on the duration of therapy revealed that shorter treatment duration (less than eight weeks)

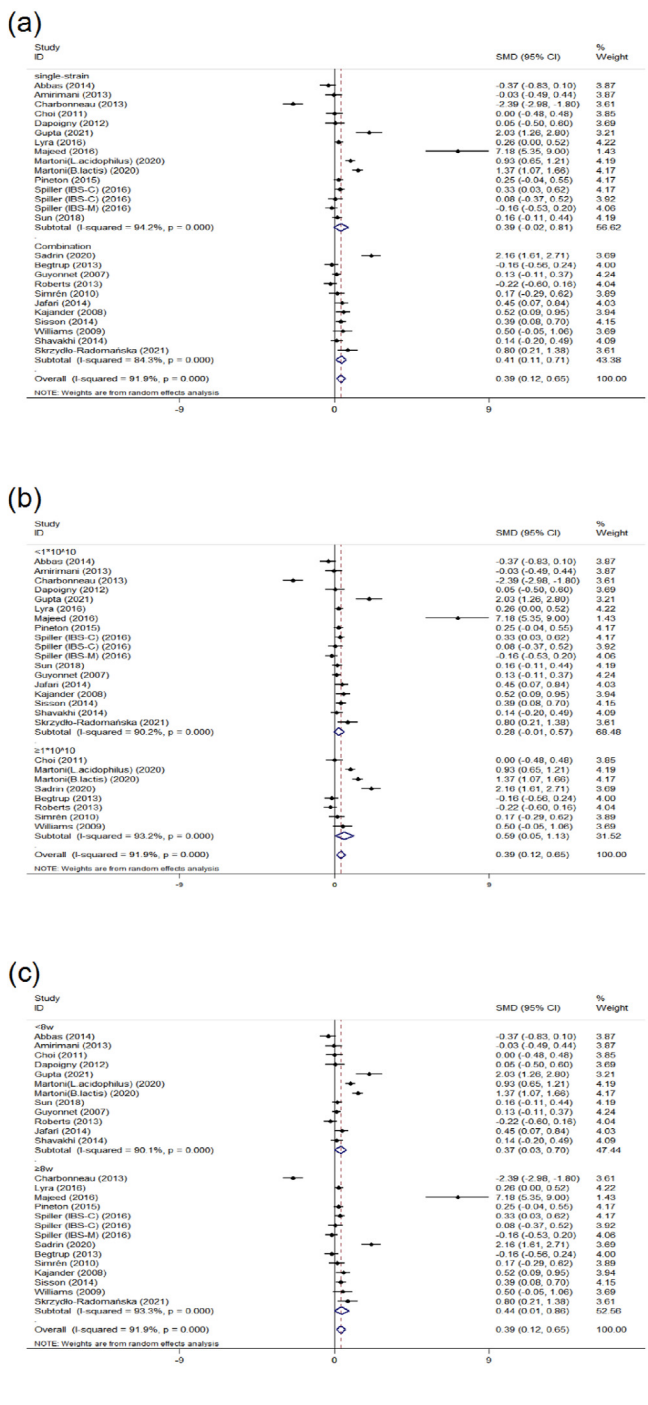

Fig. 6. Forest plot of efficacy on abdominal pain scores: subgroup of (a) treatment type, (b) daily doses of probiotics and (c) duration of therapy.

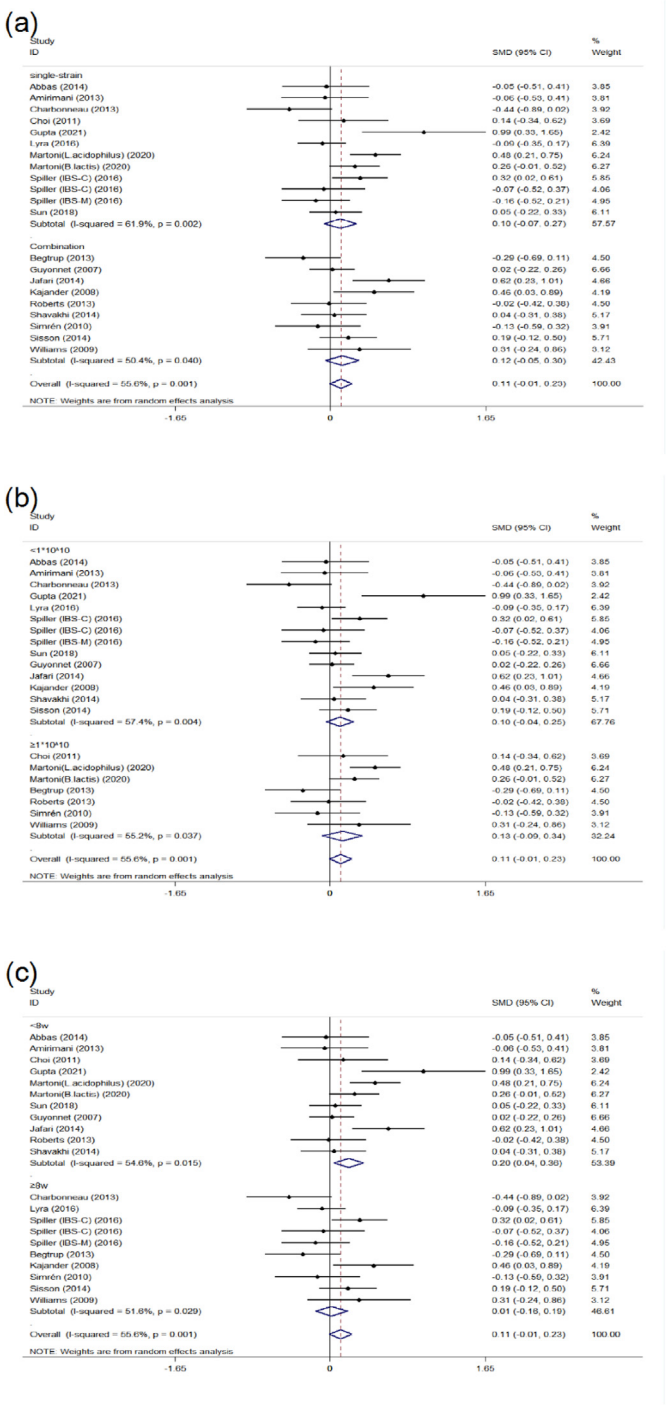

Fig. 7. Forest plot of efficacy on distension scores: subgroup of (a) treatment type, (b) daily doses of probiotics and (c) duration of therapy.

significantly reduced distension scores (SMD = 0.197, 95% CI = 0.038–0.356, P = 0.015), whereas no significant difference was observed (SMD = 0.014, 95% CI = −0.158–0.186, P = 0.029; Fig. 7) in longer duration subgroup (≥ eight weeks). Furthermore, subgroup analysis by the treatment type and probiotics daily dose yielded the same result and did not explain inter-study heterogeneity.

3.7. Efficacy of probiotics on quality of life scores

A total of 13 RCTs involving 1755 patients reported the efficacy of probiotics on irritable bowel syndrome-related quality of life scores, indicating that probiotics significantly improved the quality of life compared with placebo (SMD = 0.286, 95% CI = 0.154–0.418, P < 0.001; Fig. 8), with no significant heterogeneity (I^2 = 41.9%,

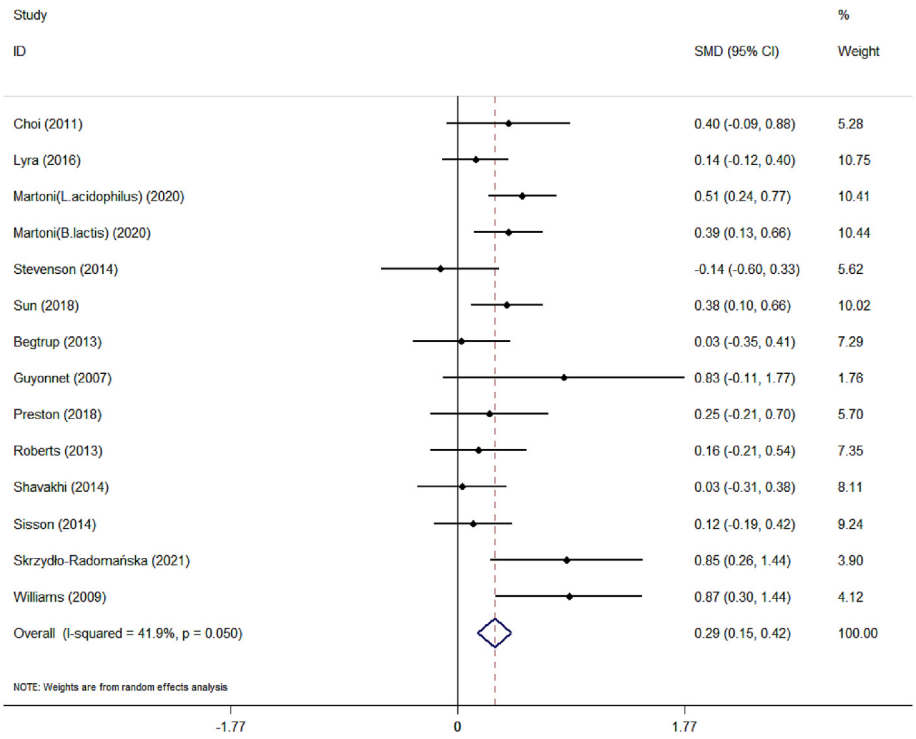

Fig. 8. Forest plot of efficacy on quality of life scores.

P = 0.05). In the subgroup analysis based on treatment type, daily probiotic doses, and duration of therapy, consistent results were observed. Interstudy heterogeneity disappeared when subgroup analyses based on treatment type and daily doses of probiotics were conducted (Figure S7). There was no significant asymmetry in the funnel plot (Begg's test, P = 0.443; Egger's test, P = 0.368; Figure S3), indicating no evidence of publication bias.

3.8. Safety of probiotics in IBS

Total adverse events were reported by 24 RCTs involving 3515 patients. Overall, 398 patients (21.7%) out of 1835 allocated to probiotics experienced any adverse event, compared with 399 patients (23.8%) out of 1680 assigned to placebo. The placebo group experienced more adverse events than the probiotics group, but the difference was insignificant (RR = 0.997, 95% CI 0.845–1.177, P = 0.973; Figure S8). No significant heterogeneity was observed between studies (I^2 = 27.4%, P = 0.107).

4. Discussion

Among various treatments for IBS, including tricyclic antidepressants, antispasmodics, and selective serotonin reuptake inhibitors, probiotics have shown beneficial effects, enhancing therapeutic effects and reducing the risk of adverse events [62,63]. Numerous pieces of evidence indicate that probiotics are potentially promising methods for modifying the gut microbiota and alleviating symptoms of functional bowel disorders, such as flatulence, bloating, and altered bowel habits [64]. The current article is the first systematic review and meta-analysis of IBS patients meeting all diagnostic criteria. It utilizes subgroup analyses of duration, daily doses, and treatment type to assess the efficacy and safety of probiotics in IBS.

Our meta-analysis indicated that probiotics may be more effective than placebo in ameliorating IBS symptoms and enhancing quality of life. Interestingly, probiotics improved the global symptom improvement rate quantitatively without changing global symptom scores qualitatively. This may be due to different studies not using a uniform evaluation scale with varying numerical ranges. Different definitions of IBS symptom improvement may limit the reported benefits of probiotics for IBS patients and lead to some heterogeneity among studies. Future research must utilize at least one global improvement measure to develop standardized IBS results to compare different experimental outcomes. When probiotics are administered in high doses or multiple strains, they alleviate abdominal pain. Due to the diversity of probiotic combinations, we could not determine the most effective probiotic combination. Different doses of probiotics may affect their effectiveness. Therefore, future research should concentrate on probiotics with a fixed dose. We found that a shorter treatment duration (less than eight weeks) could reduce distension scores [65]. Long-term and sustained use of probiotics seems to improve irritable bowel symptoms, as it takes time for the probiotics to colonize in the host's gut and reach a high population density. Abhari et al. [66] performed a randomized, double-blind, placebo-controlled trial to investigate whether the addition of *Bacillus coagulans* probiotic supplement to a low FODMAP diet is more effective than a low FODMAP diet alone in managing IBS symptoms, the results suggest that the supplement of *Bacillus coagulans* probiotic supplement to a low FODMAP diet might be superior to a low FODMAP diet alone in reducing IBS symptoms. Recent research indicated that a shorter treatment duration appeared to be more effective, possibly due to the higher number of dropouts in the longer-duration group and the limited number of studies in this regard. This may have influenced the research results, causing greater improvement in the shorter-duration group. Although there were no significant differences in adverse events between the various intervention methods, indicating that probiotics were safe for IBS patients, their long-term safety and efficacy must still be evaluated. Future research should conduct the necessary follow-ups to determine recurrence rates.

Most included RCTs assessed adherence to regimens qualitatively through verbal questioning. Moreover, subject populations varied in terms of diagnostic criteria and geographic region ranges, and most patients were instructed to maintain their usual dietary pattern without formal dietary evaluation. Therefore, the effectiveness of probiotics may be affected by ethnicity, living environment, and diet.

Several trials in our study were of insufficient quality and had small sample sizes, indicating that their efficacy was probably underpowered. It is difficult to provide a more comprehensive subgroup analysis to determine the exact source of inter-study heterogeneity due to the insufficiency of trials incorporating specific IBS subtypes. Due to the 2016 revision of the diagnostic criteria for IBS to Rome IV, future research should utilize this basis for IBS diagnosis and report efficacy data for IBS subtypes.

5. Conclusion

In summary, probiotic supplementation significantly improved IBS symptoms, including global symptom improvement rate, abdominal pain score, and quality of life score. Moreover, changing the behavior of the gut microbiota by administering a combination of probiotics and high-dose probiotics resulted in greater improvement in abdominal pain. To address the significant inter-study heterogeneity, future large-scale efficacy trials should focus on adopting unified symptom-scoring standards, incorporating consistent diagnostic criteria, monitoring dietary patterns, and investigating the impact of different probiotic combinations on IBS.

Data availability statement

All datasets generated for this study are included in the article/Supplementary Material.

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This study was unfunded.

Author contributions

Yang and Xi conceived and designed this study. Yang and Jiang searched and selected studies. Jiang and Zhao extracted essential information. Yang, Jiang and Zhao independently reviewed and scored all reviewed papers and all had access to all data; Yang and Ouyang performed statistical analyses and interpreted the pooled results. Yang, Xi, and Ouyang drafted the manuscript and all authors reviewed and contributed to the final manuscript. All authors verified the underlying data and approved the final manuscript.

Declaration of competing interest

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2024.02.025.

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