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Efficacy of Probiotics in Irritable Bowel Syndrome: Systematic Review and Meta-analysis

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e15. Learning Objective: Upon completion of this CME activity, successful learners will be able to understand the efficacy and safety of probiotics in treating symptoms of irritable bowel syndrome.

BACKGROUND & AIMS: Some probiotics may be beneficial in irritable bowel syndrome (IBS), but differences in species and strains used, as well as endpoints reported, have hampered attempts to make specific recommendations as to which should be preferred. We updated our previous meta-analysis examining this issue. **METHODS:** MEDLINE, EMBASE, and the Cochrane Controlled Trials Register were searched (up to March 2023). Randomized controlled trials (RCTs) recruiting adults with IBS, comparing probiotics with placebo were eligible. Dichotomous symptom data were pooled to obtain a relative risk of global symptoms, abdominal pain, or abdominal bloating or distension persisting after therapy, with a 95% confidence interval (CI). Continuous data were pooled using a standardized mean difference with a 95% CI. Adverse events data were also pooled. **RESULTS:** We identified 82 eligible trials, containing 10,332 patients. Only 24 RCTs were at low risk of bias across all domains. For global symptoms, there was moderate certainty in the evidence for a benefit of *Escherichia* strains, low certainty for *Lactobacillus* strains and *Lactobacillus plantarum* 299V, and very low certainty for combination probiotics, LacClean Gold S, Duolac 7s, and *Bacillus* strains. For abdominal pain, there was low certainty in the evidence for a benefit of *Saccharomyces cerevisae* I-3856 and *Bifidobacterium* strains, and very low certainty for combination probiotics, *Lactobacillus*, *Saccharomyces*, and *Bacillus* strains. For abdominal bloating or distension there was very low certainty in the evidence for a benefit of combination probiotics and *Bacillus* strains. The relative risk of experiencing any adverse event, in 55 trials, including more than 7000 patients, was not significantly higher with probiotics. **CONCLUSIONS:** Some combinations of probiotics or strains may be beneficial in IBS. However, certainty in the evidence for efficacy by GRADE criteria was low to very low across almost all of our analyses.

Keywords: Irritable Bowel Syndrome; Meta-analysis; Probiotics; Abdominal Pain; Abdominal Bloating.

Irritable bowel syndrome (IBS) is a disorder of gut-brain interaction, characterized by abdominal pain in association with abnormal stool form or frequency.[1,2] The condition affects approximately 5% of the global population,[3,4] and has a substantial impact on the individual, the health service, and society as a whole. People with IBS have reduced social functioning and impaired quality of life, to a similar or worse degree to that seen in people with organic disease.[5] Direct costs to the health service are substantial, estimated to be in excess of £1 billion in the United Kingdom,[6] and ability to work is impaired,[7] leading to other costs to society. People with IBS would accept considerable risks from a hypothetical medication in return for cure of their symptoms.[8]

Because the pathophysiology of IBS remains incompletely understood,[9] medical treatment is usually based on targeting the principal symptom(s) reported by the patient.[10] However, even when drugs are directed to the predominant abnormality of bowel habit experienced, their efficacy is modest.[11,12] The fact that approximately 10% of people with IBS report that their symptoms commenced after an acute enteric infection,[13] known as postinfection IBS, has led to the concept that alterations in the gut microbiome may be involved in its pathophysiology. Some investigators have reported that small intestinal bacterial overgrowth may be present in people with symptoms suggestive of IBS,[14] and others have shown that the colonic microbiome is altered in patients with IBS, when compared with healthy controls.[15–18] In addition, treatments that change the microbiota, such as antibiotics or fecal microbiota transplant,[19,20] may be beneficial in a subset of patients with IBS.

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host."[21] Although multiple probiotics have been tested in IBS in randomized controlled trials (RCTs), understanding of

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Abbreviations used in this paper: **CI, confidence interval; FDA, Food and Drug Administration; IBS, irritable bowel syndrome; IBS-C, irritable bowel syndrome with constipation; IBS-D, irritable bowel syndrome with diarrhea; RCT, randomized controlled trial; RR, relative risk; SD, standard deviation; SMD, standardized mean difference.**

Most current article

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Irritable bowel syndrome is a chronic disorder of gut-brain interaction that impacts greatly on the quality of life of patients. Probiotics may be efficacious for treatment but the evidence is conflicting.

NEW FINDINGS

For global symptoms, there was moderate certainty for benefit of *Escherichia* strains, low certainty for *Lactobacillus* strains and *Lactobacillus plantarum* 299V, and very low certainty for combination probiotics and *Bacillus* strains. For abdominal pain, there was low certainty for benefit of *Saccharomyces cerevisiae* I-3856 and *Bifidobacterium* strains, and very low certainty for combination probiotics, *Lactobacillus*, *Saccharomyces*, and *Bacillus* strains.

LIMITATIONS

Few trials were low risk of bias and there was heterogeneity between studies and evidence of publication bias in some of our analyses.

CLINICAL RESEARCH RELEVANCE

Future randomized controlled trials could focus on some of the species and strains, or combinations thereof, that appear promising from the data reported here but should also report their methodology and data analysis in sufficient detail to remove any concerns about potential within-trial bias.

BASIC RESEARCH RELEVANCE

Future studies could focus on some of the species and strains, or combinations thereof, to establish the mechanism(s) in which they help alleviate symptoms of irritable bowel syndrome.

which probiotics may be beneficial is limited. We, and others, have attempted to resolve these uncertainties in previous evidence synthesis exercises examining the efficacy of probiotics in IBS,[10,22–28] but because of the limited number of trials reporting similar outcome measures, in our own prior meta-analyses we pooled global symptoms and abdominal pain together as a single endpoint.[22–24] This, together with the small size of some trials, and the multitude of strains, species, and doses of probiotic used in individual RCTs, means that making recommendations concerning which probiotics, or combinations of probiotics, are beneficial according to IBS subtype or individual symptom has been difficult to date. In an attempt to resolve remaining uncertainties, we performed an updated systematic review and meta-analysis incorporating all newly identified trials since the prior version,[24] and evaluating the following as separate efficacy endpoints: global symptoms, abdominal pain, and abdominal bloating or distension. We also assessed efficacy according to IBS subtype.

Materials and Methods

Search Strategy and Study Selection

We updated our previous systematic review and meta-analysis examining the efficacy of probiotics in IBS.[24] We searched MEDLINE (2017 to March 2023), EMBASE and EMBASE Classic (2017 to March 2023), and the Cochrane central register of controlled trials. We searched conference proceedings (Digestive Diseases Week, American College of Gastroenterology, United European Gastroenterology Week, and the Asian Pacific Digestive Week) between 2017 and 2022 to identify trials published only in abstract form. Finally, we performed a recursive search using the bibliographies of all eligible articles.

We considered RCTs examining the efficacy of at least 7 days of any probiotic, or combinations of probiotics (where more than 1 species or strain was contained within a single preparation), compared with placebo, in patients $\geq$16 years with IBS as eligible for inclusion (Supplementary Table 1). We included cross-over RCTs, if efficacy data related to the first phase, prior to cross-over, were available. The diagnosis of IBS could be based on either a physician's opinion or symptom-based diagnostic criteria, supplemented by the results of investigations to exclude organic disease, where studies deemed this necessary. Trials had to report response to therapy as either a dichotomous endpoint or continuous data. Dichotomous assessment was via an assessment of global IBS symptoms (eg, subjective adequate relief of overall IBS symptoms, or a specific threshold of improvement on a total IBS symptom score), abdominal pain, or abdominal bloating or distension after completion of therapy. Continuous data of interest were global IBS symptom scores, abdominal pain scores, or abdominal bloating or distension scores at study end. We contacted first and senior authors of studies if additional information or data were required.

We searched the literature to identify studies on IBS with the terms: *irritable bowel syndrome* and *functional diseases, colon* (both as medical subject heading [MeSH] and free text terms), and *IBS*, *spastic colon*, *irritable colon*, or *functional* adj5 *bowel* (as free text terms). We combined these using the set operator AND with studies identified with the following terms: *Saccharomyces*, *Lactobacillus*, *Bifidobacterium*, *Escherichia coli*, or *probiotics* (both as MeSH and free text terms). We applied no language restrictions. Two investigators (either Vivek C. Goodoory or Mais Khasawneh, and Alexander C. Ford) evaluated all abstracts independently. We obtained full texts of all potentially eligible papers and evaluated them according to our eligibility criteria, using predesigned forms. We translated foreign language articles, where necessary. We resolved disagreements between investigators by discussion.

Outcome Assessment

Our primary outcomes of interest were the effects of probiotics compared with placebo on persistence of global IBS symptoms, abdominal pain, or abdominal bloating or distension after completion of therapy. Our secondary outcomes of interest were the effects of probiotics on global IBS symptom scores, abdominal pain scores, or abdominal bloating or distension scores and the total number of patients experiencing 1 or more adverse events associated with probiotics vs placebo.

Data Extraction

Two reviewers (Vivek C. Goodoory or Mais Khasawneh, and Alexander C. Ford) extracted all data independently onto a Microsoft Excel spreadsheet (XP professional edition; Microsoft Corp, Redmond, WA) as dichotomous outcomes (global IBS

symptoms persistent or unimproved, abdominal pain persistent or unimproved, or abdominal bloating or distension persistent or unimproved) or mean symptom scores at study end, along with a standard deviation (SD). If studies assessed response to therapy according to dichotomous endpoints, for example a 50-point decrease in the IBS severity scoring system, or a 30% improvement in the global symptom or abdominal pain score, being achieved or not achieved, we extracted these data. Otherwise, if investigators reported mean symptom scores at baseline and mean scores at the end of treatment, along with an SD, we imputed dichotomous responder and nonresponder data, according to the methodology described by Furukawa et al.[29] For example, a 30% improvement in global symptom score is determined from the following formula: number of participants in each treatment arm at final follow-up × normal SD. The latter corresponds to (70% of the baseline mean global symptom score – follow-up mean global symptom score score) / follow-up SD. We resolved any disagreements between investigators by discussion. Where trials used different probiotic strains within the same trial or different doses of the same probiotic, we extracted these separately, wherever possible. In most cases, these RCTs used different strains of probiotics, meaning that data were pooled in separate analyses, hence placebo arms were not double counted.

We also extracted the following clinical data for each trial: setting (primary, secondary, or tertiary care–based), country of origin, probiotic used (including species and strain where applicable), duration of therapy, criteria used to define IBS, outcome measures used to define symptom improvement or cure following therapy, proportion of female patients, and proportion of patients according to predominant stool pattern (IBS with constipation [IBS-C], diarrhea [IBS-D], or mixed bowel habits). We extracted data in accordance with intention-to-treat principles, assuming all dropouts were treatment failures. However, if the number of patients randomized originally in each treatment arm was unclear, we analyzed data from all evaluable patients. For adverse events, we analyzed data using the safety population, which included patients receiving at least 1 dose of probiotic or placebo, where available.

Risk of Bias and Quality of Evidence Assessment

We used the Cochrane risk of bias tool for RCTs to assess quality and risk of bias.[30] Two investigators (Vivek C. Goodoory or Mais Khasawneh, and Alexander C. Ford) performed this independently, with disagreements resolved by discussion. We recorded the method used to generate the randomization schedule and conceal treatment allocation, as well as whether blinding was implemented for participants, personnel, and outcomes assessment, whether there was evidence of incomplete outcomes data, and whether there was evidence of selective reporting of outcomes.

Data Synthesis and Statistical Analysis

We used a random effects model to pool data to give a more conservative estimate of the efficacy of probiotics in IBS.[31] We expressed efficacy as a pooled relative risk (RR) of persistence of global symptoms, abdominal pain, or abdominal bloating or distension, with 95% confidence intervals (CIs). This approach has been shown to be the most stable, compared with an RR of improvement, or using the odds ratio.[32] For symptom endpoints, we performed subgroup analyses based on particular combinations, species, and strains of probiotic, and by IBS subtype, where these data were reported. We also reported a standardized mean difference (SMD) in global or individual IBS symptom scores at study end, with 95% CIs. Finally, we pooled adverse events data with RRs and 95% CIs.

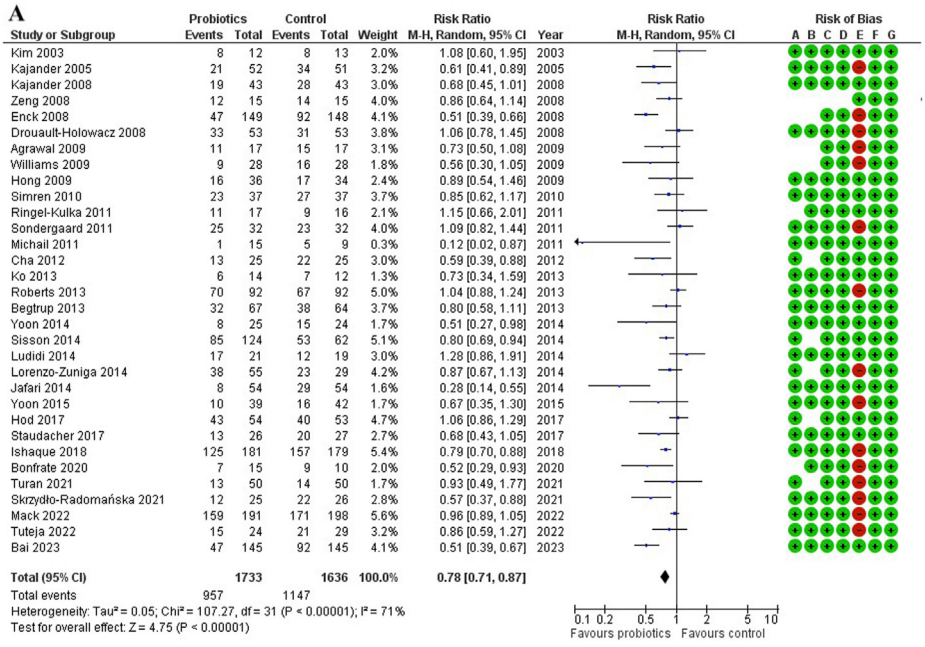
We assessed heterogeneity, which is variation between individual study results that has not occurred due to chance, using both the I^2 statistic with a cutoff of $\geq$50%, and the χ^2 test with a P value $<$.10, used to define a significant degree of heterogeneity.[33] We used Review Manager version 5.4.1 (The Cochrane Collaboration 2020)[34] to generate Forest plots of pooled RRs for primary and secondary outcomes with 95% CIs, as well as funnel plots. We assessed the latter for evidence of asymmetry, and therefore possible publication bias or other small study effects, using the Egger test,[35] if there were sufficient ($\geq$10) eligible studies included in the meta-analysis, in line with recommendations.[36] We used a P value $<$.10 to define presence of possible publication bias or other small study effects. Where there appeared to be a benefit of probiotics over placebo in analyses containing more than 1 RCT, we assessed the level of certainty of evidence according to GRADE criteria.[37] We downgraded certainty if any of high or uncertain risk of bias in individual trials, inconsistency between trial results, evidence of publication bias, or imprecision were present.

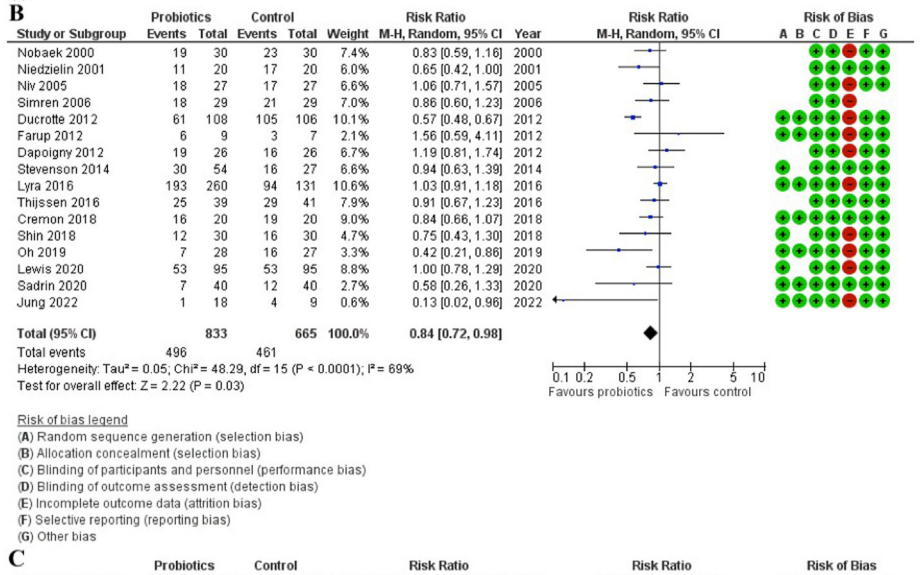
Results

We identified 1815 citations, of which 72 published articles appeared relevant, and we retrieved these for further assessment. Forty-three of these were excluded for various reasons (Supplementary Figure 1). When combined with the 53 articles included in the prior version, therefore, there were 82 eligible articles in total, as detailed in the Supplementary Materials,[e1–e82] 29 of which we identified from the updated literature search.[e42,e51,e52,e57–e82] Agreement between reviewers for assessment of newly identified trial eligibility was good (kappa statistic = 0.75). These 82 trials involved 10,332 patients. The proportion of women in trials ranged between 9% and 100%. Thirty-nine trials used a combination of probiotics, 17 *Lactobacillus* species, 9 *Saccharomyces*, 4 *Bifidobacterium*, 4 *Bacillus*, 3 either *Lactobacillus* or *Bifidobacterium*, 2 *E. coli*, 1 *Streptococcus*, 1 *Blautia*, 1 *Clostridium*, and 1 either *Lactobacillus* or a combination probiotic. Detailed characteristics of included RCTs and endpoints extracted are provided in Supplementary Table 2. Twenty-four trials were at low risk of bias across all domains (Supplementary Table 3).[e4,e6,e11,e15,e16,e20,e22,e24–e26,e35,e36,e38,e39,e41,e45,e48,e55–e57,e59,e66,e71,e81]

Efficacy of Probiotics in Terms of Effect on Persistence of Global Symptoms and Global Symptom Scores

There were 32 RCTs comparing combination probiotics with placebo,[e4,e5,e13–e15,e17,e18,e20–e22,e26–e29,e35–e37,e39–e41,e43,e45,e49,e54,e56,e58,e67,e74,e75,e77,e79,e81] evaluating 3369 patients, which gave outcomes as a dichotomous variable. There was very low certainty in the evidence by GRADE criteria for a





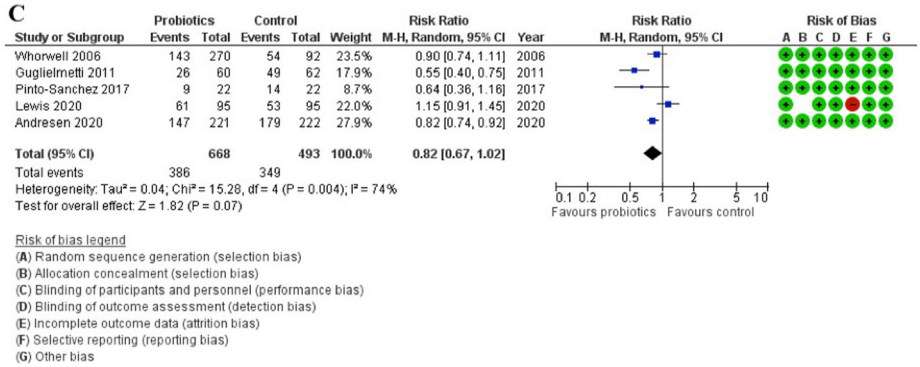


Figure 1. (*A*) Forest plot of RCTs of combination probiotics vs placebo in IBS: RR of persistence of global IBS symptoms. (*B*) Forest plot of RCTs of probiotics using *Lactobacillus* strains vs placebo in IBS: RR of persistence of global IBS symptoms. (*C*) Forest plot of RCTs of probiotics using *Bifidobacterium* strains vs placebo in IBS: RR of persistence of global IBS symptoms.

Table 1. Efficacy of Probiotics in Terms of Persistence of Global Symptoms in Irritable Bowel Syndrome

	Number of trials	Number of patients	RR of persistence of global symptoms (95% CI)	*P* value for the difference	I^2 (*P* value for χ^2)
All patients					
All combination probiotics	32	3369	0.78 (0.71–0.87)	<.001	71% (<.001)
VSL#3	4	155	0.78 (0.53–1.16)	.23	47% (.13)
Lactobacillus paracasei ssp paracasei F19, Lactobacillus acidophilus La5, and *Bifidobacterium lactis Bb12*	3	269	0.92 (0.76–1.11)	.38	14% (.31)
Enterococcus faecalis DSM16440 and *Escherichia coli DSM17252*	2	686	0.71 (0.33–1.51)	.37	97% (<.001)
LacClean Gold S	2	130	0.59 (0.37–0.93)	.02	0% (.56)
Duolac 7s	2	76	0.62 (0.43–0.89)	.009	0% (.62)
All *Lactobacillus* strains	16	1498	0.84 (0.72–0.98)	.03	69% (<.001)
Lactobacillus plantarum 299V	5	453	0.73 (0.59–0.92)	.007	59% (.04)
All *Bifidobacterium* strains	5	1161	0.82 (0.67–1.02)	.07	74% (.004)
Bifidobacterium bifidum MIMBb75	2	565	0.69 (0.46–1.04)	.07	83% (.01)
All *Bacillus* strains	3	216	0.44 (0.34–0.57)	<.001	0% (.48)
All *Saccharomyces* strains	2	469	0.94 (0.80–1.11)	.49	0% (.86)
All *Escherichia* strains	2	418	0.86 (0.79–0.93)	<.001	0% (.78)
All *Blautia* strains	1	366	0.93 (0.84–1.03)	.15	N/A
All *Clostridium* strains	1	200	0.80 (0.64–0.99)	.04	N/A
All *Streptococcus* strains	1	54	0.72 (0.53–0.99)	.04	N/A
Patients with IBS-D					
All combination probiotics	13	1272	0.78 (0.67–0.92)	.002	69% (<.001)
VSL#3	2	49	0.42 (0.04–4.85)	.49	82% (.02)
Duolac 7s	2	76	0.62 (0.43–0.89)	.009	0% (.62)
All *Lactobacillus* strains	4	157	0.57 (0.36–0.89)	.01	27% (.25)
All *Saccharomyces* strains	2	169	0.99 (0.76–1.28)	.92	0% (.81)
All *Clostridium* strains	1	200	0.80 (0.64–0.99)	.04	N/A
All *Blautia* strains	1	202	0.94 (0.82–1.08)	.36	N/A
All *Escherichia* strains	1	54	1.00 (0.57–1.74)	1.00	N/A
All *Bifidobacterium* strains	1	44	0.64 (0.36–1.16)	.14	N/A
All *Bacillus* strains	1	40	0.57 (0.31–1.05)	.07	N/A
Patients with IBS-C					
All combination probiotics	4	295	1.01 (0.89–1.14)	.87	8% (.35)
All *Saccharomyces* strains	1	180	0.82 (0.62–1.08)	.16	N/A
All *Blautia* strains	1	164	0.92 (0.78–1.07)	.26	N/A
All *Escherichia* strains	1	35	0.84 (0.41–1.73)	.64	N/A

CI, confidence interval; IBS, irritable bowel syndrome; IBS-C, IBS with constipation; IBS-D, IBS with diarrhea; N/A, not applicable; RR, relative risk.

benefit in terms of persistence of global symptoms (RR of global symptoms persisting = 0.78; 95% CI, 0.71–0.87) (Figure 1*A*, Table 1, and Supplementary Table 4), with significant heterogeneity between studies ($I^2 = 71\%$, $P < .001$), and statistically significant asymmetry detected in the funnel plot (Egger test, $P = .02$), suggesting publication bias or other small study effects. In terms of the different combinations tested (Table 1), 4 RCTs used VSL#3 in 155 patients, which was no more efficacious than placebo (RR, 0.78; 95% CI, 0.53–1.16).[e4,e26,e56,e79] Three trials used the same combination of *Lactobacillus paracasei* ssp *paracasei* F19, *Lactobacillus acidophilus* La5, and *Bifidobacterium lactis* Bb12 in 269 patients,[e22,e28,e35] with no benefit over placebo (RR, 0.92; 95% CI, 0.76–1.11). Two RCTs, which when pooled together demonstrated efficacy, used a combination of *Bifidobacterium longum*, *B. bifidum*, *B. lactis*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, and *Streptococcus thermophiles*, known as LacClean Gold S, in 130 patients (RR, 0.59; 95% CI, 0.37–0.93).[e45,e49] By GRADE criteria, certainty in the evidence was very low (Supplementary Table 5). There was very low certainty in evidence for a benefit of a 7-strain combination of 3 *Bifidobacterium*, 3 *Lactobacillus*, and 1 *Streptococcus*, Duolac 7s, in 2 trials in 76 patients (RR, 0.62; 95% CI, 0.43 to 0.89) (Supplementary Table 6).[e29,e36] Although global symptom scores were lower with combination probiotics than placebo in 20 trials containing 1685 patients (SMD, −0.36; 95% CI, −0.52 to −0.20) (Supplementary Figure 2 and Supplementary Table 7), none of the different combinations, when assessed individually, was superior to placebo.

There was low certainty in the evidence for a benefit of *Lactobacillus* strains, used in 16 trials (1498 patients),[e2,e3,e7,e10,e31–e33,e44,e47,e50,e57,e60,e65,e69,e71,e76] compared with placebo (RR, 0.84; 95% CI, 0.72–0.98) (Figure 1*B*, Table 1, and

Supplementary Table 8), with significant heterogeneity between studies (I^2 = 69%; P < .001) but no funnel plot asymmetry (Egger test, P = .53). When only the 5 RCTs that used *Lactobacillus plantarum* 299V were considered in the analysis,[e2,e3,e10,e32,e44] which contained 453 subjects, the RR of symptoms persisting was again lower with active therapy (0.73; 95% CI, 0.59–0.92) (Table 1), although heterogeneity persisted (I^2 = 59%; P = 0.04). Certainty in the evidence was low (Supplementary Table 9). *Lactobacillus* strains were no more efficacious than placebo for continuous global symptom scores in 8 trials containing 542 patients (SMD, −0.01; 95% CI, −0.18 to 0.16) (Supplementary Figure 2 and Supplementary Table 7). In pooled data, *L. plantarum* 299V also had no effect on continuous global symptom scores.

Bifidobacterium strains were studied in 5 RCTs (1161 patients),[e11,e24,e55,e66,e69] with no benefit over placebo (RR, 0.82; 95% CI, 0.67–1.02) (Figure 1*C* and Table 1). Two trials used the same strain, *B. bifidum* MIMBb75, in 565 patients, but this was not superior to placebo (RR, 0.69; 95% CI, 0.46–1.04) (Table 1).[e24,e66] However, when only the 4 trials at low risk of bias across all domains were studied, global symptoms were improved (RR, 0.76; 95% CI, 0.63–0.93).[e11,e24,e55,e66] *Bifidobacterium* strains were no more efficacious than placebo for continuous global symptom scores in 4 trials containing 666 patients (SMD, –0.27; 95% CI, –0.72 to 0.18) (Supplementary Figure 2 and Supplementary Table 7).

Certainty in the evidence was very low for a benefit of *Bacillus* strains over placebo in 3 RCTs, containing 216 patients (RR, 0.44; 95% CI, 0.34–0.57) (Table 1 and Supplementary Table 10).[e59,e64,e73] When continuous data were pooled, global symptom scores were lower with *Bacillus* strains in 2 trials containing 148 patients (SMD, −1.43; 95% CI, −2.47 to −0.39) (Supplementary Figure 2 and Supplementary Table 7). *Saccharomyces cerevisiae* was used in 2 RCTs,[e23,e53] containing 469 patients, but was not superior to placebo (RR, 0.94; 95% CI, 0.80–1.11) and *Escherichia* strains were assessed in 2 trials (418 patients),[e19,e34] with moderate certainty in the evidence for a benefit compared with placebo (RR, 0.86; 95% CI, 0.79–0.93) (Table 1 and Supplementary Table 11). Results of other single species trials are reported in Table 1 and all dichotomous results for persistence of global symptoms in Supplementary Figure 3.

Efficacy of Probiotics in Terms of Effect on Persistence of Global Symptoms According to IBS Subtype

There were 13 RCTs of combination probiotics in 1272 patients with IBS-D.[e4,e17,e26,e27,e29,e36,e40,e49,e54,e58,e74,e77,e81] Overall, global symptoms were improved with combination probiotics in IBS-D (RR, 0.78; 95% CI, 0.67–0.92) (Table 1), with significant heterogeneity between studies (I^2 = 69%; P < .001) but no evidence of funnel plot asymmetry (Egger test, P = .28). Two trials used VSL#3 in 49 patients, which was no more efficacious than placebo (RR, 0.42; 95% CI, 0.04–4.85),[e4,e26] and 2 RCTs Duolac 7s in 76 patients, with an improvement in global symptoms (RR, 0.62; 95% CI, 0.43–0.89).[e29,e36] There were 4 trials using *Lactobacillus* strains, again with an improvement in global symptoms in 157 patients (RR, 0.57; 95% CI, 0.36–0.89).[e31,e60,e65,e76] Other results are provided in Table 1. There were only 7 trials conducted in patients with IBS-C,[e18,e34,e37,e49,e53,e77,e82] and none of the combinations of probiotics or individual species were superior to placebo (Table 1).

Efficacy of Probiotics in Terms of Effect on Persistence of Abdominal Pain and Abdominal Pain Scores

There were 32 separate trials of combination probiotics that reported efficacy in terms of persistence of abdominal pain,[e4,e5,e9,e12–e14,e17,e18,e20–22,e26,e28–e30,e35,e36,e42,e43,e45,e48,e49,e52,e54,e58,e67,e72,e74,e75,e77,e79,e81] containing 3469 patients. There was very low evidence of certainty for a benefit of combination probiotics for abdominal pain (RR of persistence of abdominal pain, 0.72; 95% CI, 0.64–0.82) (Figure 2*A*, Table 2, and Supplementary Table 12) with significant heterogeneity between studies (I^2 = 72%; P < .001) and funnel plot asymmetry (Egger test, P = .003). When data were pooled from trials using the same combination, none of the individual combinations were superior to placebo (Table 2). Abdominal pain scores were lower with combination probiotics than placebo in 25 trials containing 2043 patients (SMD, –0.30; 95% CI, –0.45 to –0.14) (Supplementary Figure 4 and Supplementary Table 13), but again none of the different combinations considered alone was superior to placebo.

Eleven trials evaluated *Lactobacillus* strains in 1183 patients,[e2,e3,e16,e50,e52,e57,e65,e70,e71,e76,e80] with very low certainty in the evidence for a benefit over placebo (RR, 0.59; 95% CI, 0.45–0.76) (Figure 2*B*, Table 2, and Supplementary Table 14). There was significant heterogeneity between studies (I^2 = 73%; P < .001) and evidence of funnel plot asymmetry (Egger test, P = .02). Three RCTs used *L. plantarum* 299V in 220 patients,[e2,e3,e80] with no benefit (RR, 0.45; 95% CI, 0.15–1.35) (Table 2). Abdominal pain scores were lower with *Lactobacillus* strains than placebo in 7 trials containing 888 patients (SMD, −0.32; 95% CI, −0.52 to −0.13) (Supplementary Figure 4 and Supplementary Table 13), and with *L. plantarum* 299V in 3 trials containing 364 patients (SMD, −0.47; 95% CI, −0.68 to −0.27).

Nine trials used *Saccharomyces* strains in 1744 patients,[e23,e25,e38,e46,e53,e62,e63,e68,e78] with very low certainty in the evidence for a benefit over placebo (RR, 0.75; 95% CI, 0.57–0.99) (Figure 2*C*, Table 2, and Supplementary Table 15), with significant heterogeneity between studies (I^2 = 89%; P < .001). This effect was limited to *Saccharomyces cerevisae* I-3856, used in 5 RCTs in 1482 patients (RR, 0.64; 95% CI, 0.45 to 0.90) (Table 2),[e46,e53,e63,e68,e78] with low certainty in the evidence (Supplementary Table 16). *Saccharomyces* strains were no more efficacious than placebo for continuous abdominal pain scores in 6 trials containing 510 patients (SMD, −0.47; 95% CI, −1.13 to 0.20) (Supplementary Figure 4 and Supplementary Table 13), with no effect by strain.

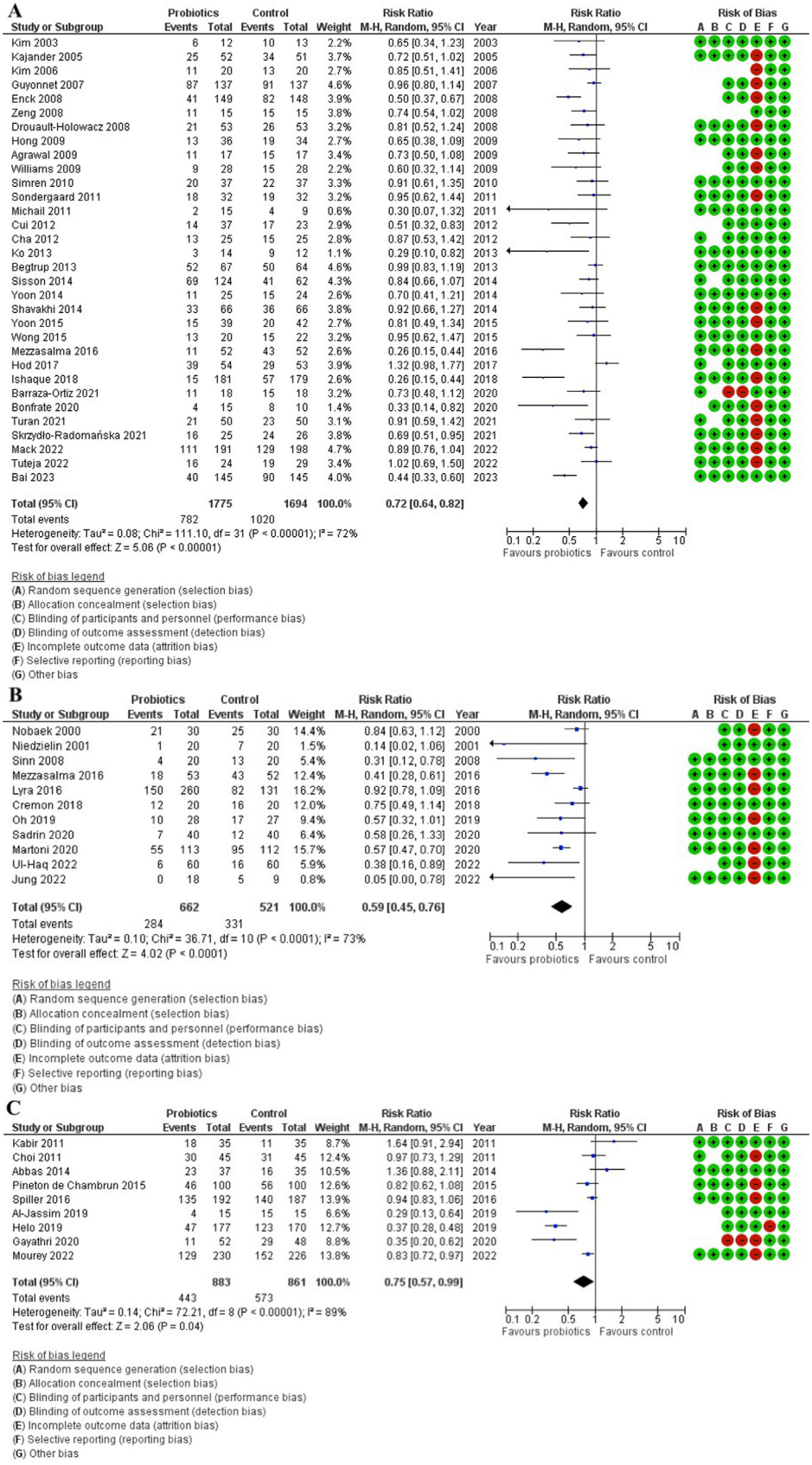


Figure 2. (*A*) Forest plot of RCTs of combination probiotics vs placebo in IBS: RR of persistence of abdominal pain. (*B*) Forest plot of RCTs of probiotics using *Lactobacillus* strains vs placebo in IBS: RR of persistence of abdominal pain. (*C*) Forest plot of RCTs of probiotics using *Saccharomyces* strains vs placebo in IBS: RR of persistence of abdominal pain.

Table 2. Efficacy of Probiotics in Terms of Persistence of Abdominal Pain in Irritable Bowel Syndrome

	Number of trials	Number of patients	RR of persistence of abdominal pain (95% CI)	*P* value for the difference	I^2 (*P* value for χ^2)
All combination probiotics	32	3469	0.72 (0.64–0.82)	<.001	72% (<.001)
VSL#3	4	144	0.87 (0.64–1.18)	.36	19% (.29)
Lactobacillus paracasei ssp paracasei F19, Lactobacillus acidophilus La5, and *Bifidobacterium lactis Bb12*	3	269	0.97 (0.83–1.14)	.74	0% (.91)
Enterococcus faecalis DSM16440 and *Escherichia coli DSM17252*	2	686	0.67 (0.37–1.22)	.19	92% (<.001)
Bifidobacterium animalis DN173 010, *Streptococcus thermophilus*, and *Lactobacillus bulgaricus*	2	308	0.89 (0.70–1.12)	.32	33% (.22)
LacClean Gold S	2	130	0.76 (0.52–1.10)	.14	0% (.72)
Duolac 7s	2	76	0.55 (0.18–1.65)	.28	73% (.05)
All *Lactobacillus* strains	11	1183	0.59 (0.45–0.76)	<.001	73% (<.001)
Lactobacillus plantarum 299V	3	220	0.45 (0.15–1.35)	.16	78% (.010)
All *Saccharomyces* strains	9	1744	0.75 (0.57–0.99)	.04	89% (<.001)
Saccharomyces cerevisiae I-3856	5	1482	0.64 (0.45–0.90)	.01	93% (<.001)
Saccharomyces boulardii	3	232	1.21 (0.87–1.67)	.26	44% (.17)
All *Bifidobacterium* strains	3	389	0.78 (0.64–0.95)	.02	37% (.20)
All *Bacillus* strains	3	212	0.33 (0.23–0.47)	<.001	10% (.33)
All *Blautia* strains	1	366	0.92 (0.79–1.06)	.25	N/A
All *Escherichia* strains	1	298	0.87 (0.79–0.95)	.002	N/A
All *Clostridium* strains	1	200	0.93 (0.76–1.14)	.49	N/A

CI, confidence interval; N/A, not applicable; RR, relative risk.

Finally, there were 3 trials of *Bifidobacterium* strains in 389 patients,[e24,e55,e70] and 3 trials of *Bacillus* strains in 212 patients.[e51,e64,e73] Certainty in the evidence for a benefit over placebo for persistence of abdominal pain was low (RR, 0.78; 95% CI, 0.64 to 0.95) and very low (RR, 0.33; 95% CI, 0.23 to 0.47), respectively (Table 2 and Supplementary Tables 17 and 18). *Bifidobacterium* strains were no more efficacious than placebo for abdominal pain scores in 4 trials containing 539 patients (SMD, −0.35; 95% CI, −0.70 to 0.00) but abdominal pain scores were lower with *Bacillus* strains in 3 trials containing 177 patients (SMD, −1.62; 95% CI, −2.36 to −0.87) (Supplementary Figure 4 and Supplementary Table 13). Results of other single species trials are reported in Table 2 and all dichotomous results for persistence of abdominal pain in Supplementary Figure 5.

Efficacy of Probiotics in Terms of Effect on Persistence of Abdominal Bloating or Distension and Abdominal Bloating or Distension Scores

Twenty-six trials of combination probiotics,[e4–e6,e9,e12,e17,e18,e21,e22,e26,e28–e30,e35,e36,e42,e43,e45,e48,e49,e52,e58,e67,e74,e75,e79] containing 2222 patients, reported effect of probiotics on abdominal bloating or distension (Table 3). Overall, there was very low certainty in the evidence for a benefit of combination probiotics over placebo (RR of persistence of abdominal bloating or distension = 0.75; 95% CI, 0.64 to 0.88) (Figure 3 and Supplementary Table 19), with significant heterogeneity between studies (I^2 = 78%, P < 0.001) and funnel plot asymmetry (Egger test, P = .003). Pooling data from trials that used the same combination of probiotics did not demonstrate any efficacious combination (Table 3). Abdominal bloating or distension scores were lower with combination probiotics than placebo in 25 trials containing 1976 patients (SMD, −0.23; 95% CI, −0.39 to −0.07) (Supplementary Figure 6 and Supplementary Table 20). Again, none of the different combinations alone was superior to placebo.

Five trials used *Lactobacillus* strains in 723 patients,[e50,e52,e71,e76,e80] and 5 trials *Saccharomyces* strains in 641 patients.[e23,e25,e38,e53,e62] Neither demonstrated a benefit for abdominal bloating or distension (RR, 0.67; 95% CI, 0.43 to 1.04 and 0.87; 95% CI, 0.64 to 1.17, respectively) (Table 3). *Lactobacillus* strains were not superior to placebo for continuous abdominal bloating or distension scores in 5 trials containing 606 patients (SMD, −0.13; 95% CI, −0.30 to 0.04) (Supplementary Figure 6 and Supplementary Table 20). *Saccharomyces* strains were also no more efficacious than placebo in 4 trials containing 239 patients (SMD, −0.92; 95% CI, −2.00 to 0.17) (Supplementary Figure 6 and Supplementary Table 20).

There was very low certainty in the evidence for a benefit of *Bacillus* strains in 3 RCTs containing 212 patients (RR, 0.41; 95% CI, 0.31 to 0.56) (Table 3 and Supplementary

Table 3. Efficacy of Probiotics in Terms of Persistence of Abdominal Bloating or Distension in Irritable Bowel Syndrome

	Number of trials	Number of patients	RR of persistence of abdominal bloating or distension (95% CI)	*P* value for the difference	I^2 (*P* value for χ^2)
All combination probiotics	26	2222	0.75 (0.64–0.88)	<.001	78% (<.001)
VSL#3	5	192	0.65 (0.42–1.02)	.06	52% (.08)
Lactobacillus paracasei ssp paracasei F19, Lactobacillus acidophilus La5, and *Bifidobacterium lactis Bb12*	3	269	1.02 (0.89–1.18)	.78	0% (.92)
Bifidobacterium animalis DN173 010, *Streptococcus thermophilus*, and *Lactobacillus bulgaricus*	2	308	0.86 (0.60–1.26)	.45	71% (.06)
LacClean Gold S	2	130	0.98 (0.67–1.45)	.94	8% (.30)
Duolac 7s	2	76	0.94 (0.61–1.47)	.80	0% (.88)
All *Lactobacillus* strains	5	723	0.67 (0.43–1.04)	.07	88% (<.001)
All *Saccharomyces* strains	5	641	0.87 (0.64–1.17)	.34	60% (.04)
Saccharomyces boulardii	3	232	0.97 (0.77–1.23)	.80	0% (.79)
All *Bacillus* strains	3	212	0.41 (0.31–0.56)	<.001	0% (.83)
All *Clostridium* strains	1	200	0.97 (0.81–1.16)	.75	N/A
All *Bifidobacterium* strains	1	122	0.66 (0.49–0.88)	.005	N/A

CI, confidence interval; N/A, not applicable; RR, relative risk.

Table 21).[e51,e64,e73] Abdominal bloating or distension scores were also lower with *Bacillus* strains than placebo in 3 trials containing 177 patients (SMD, −1.26; 95% CI, −2.27 to −0.25) (Supplementary Figure 6 and Supplementary Table 20). Although there was an improvement in abdominal bloating or distension with *B. bifidum* MIMBb75 in 1 RCT (RR, 0.66; 95% CI, 0.49 to 0.88),[e24] *Bifidobacterium* strains were no more efficacious than placebo for continuous abdominal bloating or distension scores in 3 trials containing 501 patients (SMD, −0.30; 95% CI, −0.68 to 0.09) (Supplementary Figure 6 and Supplementary Table 20). Results of other single species trials are reported in Table 3 and all dichotomous results for persistence of abdominal bloating or distension in Supplementary Figure 7.

Adverse Events

Total adverse events were reported by 55 RCTs,[e1–e7,e9,e12,e14–e17,e19–e24,e26,e29,e31,e32,e34,e35,e38–e40,e42–e48,e50,e51,e53,e58,e59,e61,e64–e68,e71–e75,e77,e78,e81,e82] containing 7448 patients. The RR of experiencing any adverse event was not significantly higher with probiotics (1.05; 95% CI, 0.90–1.22), with significant heterogeneity between studies ($I^2 = 34\%$, $P = .03$), and evidence of funnel plot asymmetry (Egger test, $P = .04$).

Discussion

This updated systematic review and meta-analysis has demonstrated that some combinations of probiotics, or specific species and strains, have beneficial effects in IBS. As in our previous meta-analyses, we found some evidence to support the use of some probiotics for global IBS symptoms, abdominal pain, and abdominal bloating or distension. For global symptoms, there was moderate certainty in the evidence for a benefit of *Escherichia* strains, low certainty for *Lactobacillus* strains and *L. plantarum* 299V, and very low certainty for combination probiotics, LacClean Gold S, Duolac 7s, and *Bacillus* strains. For abdominal pain, there was low certainty in the evidence for a benefit of *S. cerevisiae* I-3856 and *Bifidobacterium* strains, and very low certainty for combination probiotics, *Lactobacillus*, *Saccharomyces*, and *Bacillus* strains. For abdominal bloating or distension, there was very low certainty in the evidence for a benefit of combination probiotics and *Bacillus* strains. Analyses according to stool pattern revealed a paucity of trials of probiotics in IBS-C, meaning their use in patients with subtype is less evidence-based, but combination probiotics and *Lactobacillus* strains improved global symptoms in IBS-D. Combination probiotics and *Bacillus* strains improved global symptom scores, abdominal pain scores, and abdominal bloating or distension scores, and *Lactobacillus* strains improved abdominal pain scores. In some cases, pooling data from RCTs using continuous symptom scores did not yield results that were consistent with dichotomous endpoints. This could be because of increased heterogeneity between studies, the individual ranges of the scores used, differences between treatment arms in baseline scores, or inclusion of nonoverlapping trials in each set of analyses. Finally, adverse events were no more frequent with probiotics than placebo. However, due to a combination of 1 or more of heterogeneity between studies, possible publication bias, risk of bias of studies, and modest efficacy, the level of certainty of evidence would not be graded as anything more than low or very low, according to GRADE criteria,[37] in almost all of our analyses.

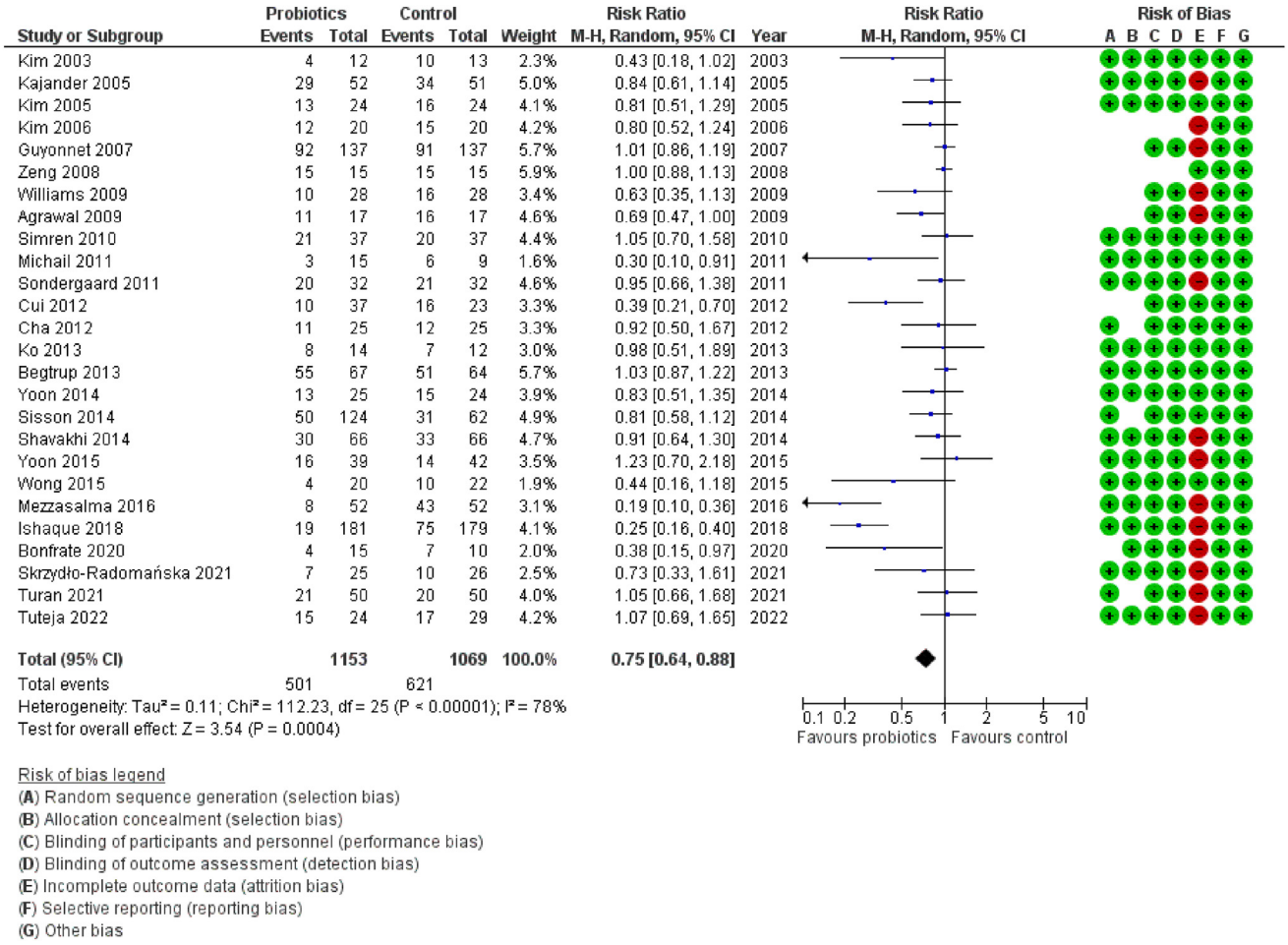


Figure 3. Forest plot of RCTs of combination probiotics vs placebo in IBS: RR of persistence of abdominal bloating or distension.

We performed independent assessment of eligibility and data extraction, in duplicate. We used an intention-to-treat analysis and pooled data with a random effects model, to minimize the likelihood that any beneficial effects of probiotics have been overestimated. We contacted investigators of potentially eligible studies to obtain either dichotomous data or continuous data and imputed dichotomous data from means and SDs to increase the number of trials reporting similar endpoints, increasing the number of trials, and participants, contributing data to each of the analyses. In our previous meta-analyses,[22–24] we were unable to draw definitive conclusions about the efficacy of specific probiotics because of a small number of trials of some combinations, species, or strains, as well as a lack of uniformity in reporting of endpoints. In this update, because we had more eligible trials and imputed data, we were able to study the efficacy of probiotics according to 3 separate dichotomous endpoints, global IBS symptoms, abdominal pain, and abdominal bloating or distension, as well as effect on global symptom scores, abdominal pain scores, and abdominal bloating or distension scores. Finally, we performed subgroup analyses to assess treatment effect according to combinations of, and individual, probiotics used, as well as predominant stool pattern.

Limitations of this systematic review and meta-analysis arise from the nature of the studies available for synthesis. Only 24 of 82 eligible RCTs were low risk of bias across all domains, and there was significant heterogeneity between trials in many of our analyses, as well as evidence of publication bias, or other small study effects, in some of our analyses. Imputing from continuous symptom data provides only an approximation of dichotomous endpoints, although the methodology we used has been shown to provide near identical RRs to those using original dichotomous data in other studies,[29] and allowed us to pool data from an additional 46 RCTs. In addition, even with the imputation of data to derive similar endpoints, the number of trials of each particular combination or strain providing data for the same endpoint was small for some of our analyses. For these reasons, performing analyses considering only low risk of bias trials would not be possible. Trial duration was short, compared with the likely chronicity of symptoms in IBS, with only 5 trials conducted over a 12-week period,[e34,e37,e43,e50,e53] which is recommended by guidelines for the design of treatment trials in IBS.[38] In addition, few studies adhered to Food and Drug Administration (FDA) endpoints recommended for IBS,[39] although as 34 trials were conducted before these were published and many RCTs

recruited mixed populations of patients, this would be difficult, as these are subtype specific. Nevertheless, we extracted data for FDA endpoints preferentially, wherever reported.

Our combining of species together could be criticized, as different strains may have different mechanisms of action and, therefore, potentially differ in efficacy. Wherever possible, we attempted to undertake subgroup analysis of trials using the same combination of probiotics or RCTs using the same species and strain. However, this issue may be particularly relevant for *Bifidobacterium* strains. Four trials of *Bifidobacterium* strains that were low risk of bias across all domains showed efficacy, or a trend toward a benefit,[e11,e24,e55,e66] for global symptoms but when pooled with a negative RCT of another strain at high risk of bias,[e69] there was no overall benefit. When only low risk of bias studies were considered in the analysis, there appeared to be a benefit of *Bifidobacterium* strains for global symptoms. Two of these trials, containing more than 500 patients, demonstrated a benefit of *B. bifidum* MIMBb75 over placebo for global symptoms,[e24,e66] but when data from these were pooled in a random effects model, the 95% CI crossed 1. Another RCT conducted in more than 300 patients using *Bifidobacterium infantis* 35624 demonstrated superiority over placebo for the 1×10^8 colony-forming units per capsule dose,[e11] but had considerable problems with the formulation of the 1×10^{10} colony-forming units per capsule dose, due to different dissolution characteristics of the capsule compared with the other 2 doses studied. Another RCT of *B. infantis* 35624 1×10^9 colony-forming units conducted in 302 individuals with abdominal discomfort or bloating at a frequency of 2 or more times per week, but who were not patients with a known diagnosis of IBS, demonstrated a significant reduction in both discomfort and bloating scores after treatment, although this was not superior to placebo.[40]

There is continued interest in the role of probiotics in the management of IBS, as evidenced by the publication of more than 20 new RCTs since the prior version of this meta-analysis in 2018. Our analyses provide some support for the use of certain probiotics in IBS, and also for particular strains for specific symptoms. However, there is a paucity of data for their use in patients with IBS-C, with only 7 RCTs reporting efficacy in this subtype, and no evidence of efficacy in any of these analyses. Their use in patients with IBS-C is, therefore, not supported by current evidence. Based on this meta-analysis, or the results of individual RCTs, combination probiotics, particularly LacClean Gold S and Duolac 7s, *Lactobacillus* strains overall, but particularly *L. plantarum* 299V, *B. bifidum* MIMBb75, *Bacillus* strains, *Escherichia* strains, *Clostridium butyricum*, and *Streptococcus faecium* were beneficial for global IBS symptoms. In terms of abdominal pain, some combination probiotics, *Lactobacillus* and *Bifidobacterium* strains, *S. cerevisiae* I-3856, and *Bacillus* and *Escherichia* strains improved symptoms. Finally, for abdominal bloating or distension, combination probiotics, *Bacillus* strains, and *B. bifidum* MIMBb75 all led to an improvement in symptoms. For the most part, probiotics were safe, with adverse events data provided by 55 trials, including more than 7000 patients.

However, caveats are applicable to most of these suggestions due to the nature of the literature available for review. If gastroenterologists are to be able to recommend probiotics to patients with confidence, a better evidence base is needed. Future RCTs could focus on some of the species and strains, or combinations thereof, that appear promising from the data reported here but they must also adhere to the recommendations for the design of treatment trials in IBS,[38] with a minimum treatment duration of 12 weeks. They should also report their methodology and data analysis in sufficient detail to remove any concerns about potential bias within the trial. In addition, even if the use of an FDA-recommended endpoint is not feasible as a primary outcome measure, they should at least consider the use of some of the FDA endpoints as secondary outcomes, particularly if they are recruiting only 1 subtype of patients with IBS. Finally, given the lack of clarity concerning efficacy of individual species, strains, or combinations thereof, dose-ranging studies, of which there have been very few to date, may help further elucidate which probiotics are beneficial in IBS.

In summary, this meta-analysis of 82 trials, containing data from more than 10,000 patients, has demonstrated moderate, low, or very low certainty evidence for a benefit of several individual probiotics, or combinations of probiotics, for particular symptoms experienced by patients with IBS. Our use of imputation and contact with original investigators allowed us to pool dichotomous data from more studies than previously, allowing us to draw more meaningful conclusions than prior evidence synthesis exercises in this field where, for the most part, no recommendations concerning efficacy of particular combinations of probiotics or strains could be made. The fact that few of the included studies were low risk of bias across all domains should be borne in mind when making treatment recommendations. As a result of this, and other factors, certainty in the evidence by GRADE criteria was low to very low across almost all our analyses.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.07.018.

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Data Availability
Data used in this meta-analysis are publicly available.