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Efficacy of *Bifidobacterium infantis 35624* in patients with irritable bowel syndrome: a meta-analysis

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TRANSPARENCY

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Authors' contributions

Study concept and design: FY, HN, CVA, and JR; manuscript drafting and revision: FY, HN, CVA, MK, SW, and JR; statistical analysis: HN, and JR; data acquisition: FY, HN, and JR.

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ABSTRACT

Background:

The treatment of irritable bowel syndrome (IBS) is a challenge because its cause remains unknown. Previous clinical trials to examine the efficacy of probiotic *Bifidobacterium infantis 35624* (*B. infantis*) in patients with IBS showed inconsistent findings. This study aimed to assess the combined effect of *B. infantis* on reducing symptom severity of IBS based on the published data.

Methods:

A meta-analysis was conducted using fixed-effect models to estimate the combined effect of *B. infantis* on primary outcomes, which included abdominal pain, bloating/distention, and bowel habit satisfaction. A systemic review was performed based on PubMed, Cochrane Library, and EMBASE databases to identify the randomized controlled trials comparing probiotics *B. infantis* with placebo in treating IBS symptoms, published up until December 31, 2016. Standardized mean differences (SMD) method was used to combine data since scales to measure the efficacy of probiotics were different among studies.

Results:

A total of five studies were identified as suitable for inclusion, including three studies with single probiotic *B. infantis* and two studies with composite probiotics containing *B. infantis*. Treatment with single probiotic *B. infantis* didn't impact on abdominal pain, bloating/distention, or bowel habit satisfaction among IBS patients. However, patients who received composite probiotics containing *B. infantis* significantly reduced abdominal pain (SMD, 0.22; 95%CI, 0.03-0.41) and bloating/distention (SMD, 0.30; 95%CI, 0.04-0.56). After combining the data from six studies, the improvement of bloating/distention among IBS patients remained significant (SMD, 0.21; 95%CI, 0.07-0.35).

Conclusion:

Composite probiotics consisting of *B. infantis* might be an effective therapeutic option to IBS patients, which could significantly alleviate the symptoms of IBS without significant adverse effects. However, the efficacy of single probiotic *B. infantis* on IBS has not been confirmed yet, which needs to be further validated by more large-sized randomized clinical trials.

Key words: irritable bowel syndrome; *Bifidobacterium infantis 35624;* meta-analysis; probiotic
Short title: *B. infantis* in irritable bowel syndrome

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders usually defined by the coexistence of abdominal pain or discomfort and an alteration in bowel habit.[1,2] While IBS is not considered a life-threatening disease, IBS patients suffer from a disproportionately higher rate of co-morbidity with other disorders, such as fibromyalgia[3], chronic fatigue[4], pelvic pain[5] and psychiatric disorders[6]. Nearly 3.5 million IBS physician visits occur in the United States annually despite the fact that only about 10 percent of people with symptoms seeks help from their physicians.[7] To date, however, defining and treating IBS continues to be challenging.

Among the wide variety of treatment options, probiotics appear to be one of the best options.[8] Recently, it has been suggested that alterations in the gut microbiota, leading to many gut dysfunctions, might be a possible etiological mechanism.[9-13] In view of the new theory of alterations in the gut microbiota in IBS patients, more and more clinical trials involve examining the efficacy of diverse probiotics in IBS treatment, including *B. infantis* 35624 and various probiotic combinations.[14-18]

Although several reviews and meta-analyses have concluded that probiotics appear to improve overall IBS symptoms, the efficacy of specific probiotic species remains unclear.[19-24] Previous meta-analyses usually include numerous or any probiotics in a single review, which adds difficulty to thoroughly assess a specific species in the symptom relief of IBS patients. Therefore, we only focused on the assessment of the efficacy of *B. infantis* 35624 in alleviating IBS symptoms in this study.

METHODS

Study selection

We performed a search using PubMed, Cochrane Library, and EMBASE databases to identify the randomized controlled trials comparing probiotics *B. infantis* with placebo in treating IBS symptoms, published up until December 31, 2016. “Irritable bowel syndrome” and “Bifidobacterium” were searched as MeSH terms or keywords. If a study could not be included/excluded based on the Title/Abstract field, the full text of the article was reviewed. We also reviewed the reference lists of studies that met inclusion criteria in order to seek pertinent articles manually. Articles were independently assessed by two reviewers using predesigned eligibility forms, according to the prospectively defined eligibility criteria. Any disagreement between investigators was resolved by consensus.

Inclusion and exclusion criteria

We included the randomized controlled trials that met all the following criteria: 1) comparison of the efficacy of *B. infantis* versus placebo for patients with IBS; 2) Rome criteria I, II, or III for the diagnosis of IBS; 3) age greater than 15 years old; and 4) studies results in English or Chinese. Studies were excluded if the subjects were followed up for less than 1 week, the IBS symptoms were not assessed.

Outcome assessment

The primary outcomes assessed were the effects of *B. infantis* compared with placebo on abdominal pain, bloating/distention, and bowel habit satisfaction. Secondary outcomes included the overall IBS symptom score, the adverse effects and the tolerability during the treatment.

Abdominal pain, bloating/distention and overall IBS symptoms were measured using a 6-point scale where 0 stands for none and 5 stand for very severe. Bowel habit satisfaction was also assessed by a 6-point scale where 0 stands for very satisfied and 5 stands for very dissatisfied. For those studies that reported in a different scale (e.g. a 10-cm visual analogue scale), we transformed the results into a 6-point scale first before we combined them.

Data extraction and quality assessment

All data for each trail were extracted on to a Microsoft Excel spreadsheet (part of Microsoft Office Professional Plus 2010), including authors, year, study design, sample size, study drug (including species and doses), proportion of female patients, proportion of patients according to predominant stool pattern for IBS, inclusion and exclusion criteria, duration of therapy, duration of follow-up, primary outcome measure used to define symptom improvement or cure following therapy, total number of adverse events reported, and tolerability. The quality of retrieved studies was assessed by the Jadad scale with a maximum score of 5.[25]

Statistical analysis

Mean, standard error, and sample size data for both treatment group and control group were collected as summary statistics at the end of the treatment period. The macros %MAINVERSE and %MAFOREST, which were developed by Stephen Senn, were used to combine the results and draw a forest plot.[26] Heterogeneity between studies was assessed using Cochran's Q test, and the I^2 index was used to quantify the amount of heterogeneity, with a value greater than 50% indicating substantial heterogeneity.[27] We carried out a classic fixed-effects model (or a random-effects model in case of heterogeneity) using inverse weighting by variances of treatment contrasts because only five studies were available. Funnel plot was used to detect publication bias in trials included in the meta-analysis. All analyses were performed using the SAS 9.4 software (by SAS Institute Inc., Cary, NC, USA).

RESULTS

Quality assessment of the included studies

After searching our bibliographic database, a total of 202 studies were retrieved in our study. Then we performed a full text review, and excluded 197 trials (29 duplicate trials, 95 irrelevant studies, 72 non-randomized trials and 1 extended study from another) according to our inclusion and exclusion criteria. Thus, five studies met the inclusion criteria and were included in this meta-analysis (Figure 1).

Description of the included studies

To further clarify the effect of *B. infantis* on IBS, a systematic review covering details of the selected reference including age, sex, subtype and study drug used was summarized in Table 1. These five studies involving a total of 666 patients were included. Three of five studies use single probiotic *B. infantis* while another two studies use composite probiotics which contained *B. infantis*. All of the studies were considered as high quality based on Jadad scale (Table 1).

Improvement of clinical symptoms and signs of IBS

As shown in Table 2, treatment with single probiotic *B. infantis* did not impact abdominal pain, bloating/distention, or bowel habit satisfaction among IBS patients. However, patients who received a composite probiotic consisting of *B. infantis* had a significant reduction in abdominal pain (SMD, 0.22; 95%CI, 0.03-0.41) and bloating/distention (SMD, 0.30; 95%CI, 0.04-0.56). After combining the five studies in which patients were treated with either single probiotic *B. infantis* or composite probiotics containing *B. infantis*, the improvement of bloating/distention among IBS patients remained significant (SMD, 0.21; 95%CI, 0.07-0.35; Figure 2), but not for abdominal pain (Figure 3).

Heterogeneity among selected studies

Notable heterogeneity was found among the three studies with single probiotic *B. infantis* (I^2>50%) as examining the primary outcomes of abdominal pain, bloating/distention and bowel habit satisfaction. However, heterogeneity could be ignored between the two studies with composite probiotics (I^2<1%). Overall, no publication bias was found in this study based on the symmetric funnel plots (Figure 4).

Overall adverse effects and tolerability were evaluated in selected studies

In this study, our secondary outcomes included the adverse effects and the tolerability during the treatment. Two trials reported that there was no adverse effect with composite probiotic which contained *B. infantis*, one study reported there was no significant adverse event with *B. infantis* and two studies reported adverse effects with *B. infantis* (Supplementary Appendix).

In Whorwell's study,[15] no significant adverse events were reported in treatment group and only 17 (<5%) of all subjects withdrew because of an adverse event. In Charbonneau's group, [28] the highest proportion of subjects reporting adverse events was in the placebo group (38%) compared with 33% in the IBS probiotic treatment group and 32% in the healthy probiotic treatment group. In O'Mahony's study,[14] four subjects (5%) reported adverse events during the study but no clinically significant changes were recorded in any of the subjects during the study. In all included studies, both *B. infantis* and composite probiotic which contained *B. infantis* were overall well tolerated (Supplementary Appendix).

DISCUSSION

Major finding

Probiotics have been demonstrated to be an effective way to prevent and treat some gastrointestinal disorders.[29,30] However, inconsistent findings were obtained regarding to the efficacy of probiotics (*B. infantis*) on IBS patients or non-patients with bowel symptoms.[31] A meta-analysis including all relevant data and recent study is needed to clarify this problem. Our meta-analysis data from the included studies has demonstrated that composite probiotics consisting of *B. infantis* might be an effective therapeutic option to IBS patients, which could significantly reduce abdominal pain and improve bloating/distention without notable adverse effects. However, the efficacy of single probiotic *B. infantis* on IBS patients has not been confirmed yet.

Potential mechanisms of action of probiotics in IBS

IBS is considered a multifactorial disorder associated with visceral hypersensitivity, altered gut motility, and dysfunction of the brain-gut axis and immune system. Recent studies have also shown that patients with IBS exhibited a sustained hypothalamic–pituitary–adrenal (HPA) axis response to acute psychosocial stress,[32] while consumption of a strain of *Bifidobacterium longum* has been demonstrated to be associated with attenuated HPA axis reactivity to acute stress.[33] However, the pathophysiology of the disorder is still not completely understood.[2,32,34-36] Of those proposed mechanisms, microbiome change in the gastrointestinal tract has been supported to play a critical role in the causation and progression of IBS symptoms. [21,37-39] The consumption of probiotic bacteria may increase circulating vitamin D, which interacts with the vitamin D receptor to facilitate an effective immune response.[40] A recent report has shown that there were significantly more total bacteria in patients with IBS but with a reduction level in bifidobacteria.[41] *B. infantis* 35624, a well characterized and non-pathogenic strain, has been reported to be able to normalize the ratio of cytokines interleukin (IL)-10 to IL-12, [14-18] stimulate anti-inflammatory response, [42] inhibit the growth of pathogenic organisms and specifically relieve many symptoms of IBS. [15] In our study, single *B. infantis* 35624 was not shown to be effective among IBS patients, which might be explained by the fact that numerous probiotics need to work together in order to recover the microbiome in the gastrointestinal tract. It remains challenging to identify most or all of probiotic species and strains from the countless gut bacteria. In addition, it is still unclear if the combination treatment of probiotics and vitamin D supplement[43] could have better efficacy among IBS patients.

Clinical significance

The annual cost of IBS treatment in the United States has been estimated to be between $1.7 billion and $10 billion in direct medical costs and $20 billion for indirect costs.[44] IBS patients suffer greatly because of the symptoms of IBS, such as pain and discomfort, bloating and swelling of the abdomen and changes in stools. Recent studies have shown that probiotics appear to be efficacious in IBS [21] and bifidobacterium has been proven to alleviate symptoms in IBS [14] and improve quality of life in IBS patients. [45] As a well characterized and non-pathogenic strain, *B. infantis* 35624 has been reported to be able to specifically relieve many of the symptoms of IBS [15], but it was not confirmed in our review study. Our meta-analysis has shown that composite probiotic consisting of *B. infantis* 35624 is an effective

therapeutic option to improve abdominal pain and bloating among IBS patients, which may be used as a supplement to standard therapy.

Study limitation

This study has a few limitations: 1) only five trials were finally included in our study. Three of five trials had a small number of patients; 2) a mixture of probiotics were used in two cases, which made it difficult to establish the exact role of *B. infantis* 35624 in the management of IBS patients and to know how much contribution of *B. infantis* could be in the efficacy of composite probiotic; 3) the study of Whorwell et al.[15] showed that *B. infantis* was significantly superior to placebo only at the dosage of 1 x 10^8, while a dose range of 1 x 10^9-1 x 10^{10} was used in both the study of O'Mahony et al.[14] and Charbonneau et al.[28]; 4) the proportion of female patients was listed in our meta-analysis, but the male data may be needed in the future study; 5) notable heterogeneity was found among the three studies with single probiotic *B. infantis* (I^2>50%) and the difference in heterogeneity between single strain and composite probiotic studies seems remarkably large; 6) there was also a lack of details about the mechanism underlying the beneficial effect of *B. infantis* and other probiotics on IBS patients.

CONCLUSIONS

In this study, our meta-analysis data has shown that treatment with composite probiotics consisting of *B. infantis* on IBS patients could significantly alleviate the symptoms of IBS without significant adverse effects, but not for single probiotic *B. infantis*. Because of the limitations of this meta-analysis, more large-sized randomized clinical trials are still needed to prove the efficacy of *B. infantis* on IBS. Future studies are also expected to examine the long-term therapeutic effect of *B. infantis* and other probiotics on IBS patients, and further explore the mechanism underlying the beneficial effect of them.

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Figure 1. Summary of the study selection and exclusion processes

Figure 2. Forest plot for bloating/distention based on the five studies

Figure 3. Forest plot for abdominal pain based on the five studies

Figure 4. Funnel plots for abdominal pain and bloating/distention based on the five studies

Figure 1. Summary of the study selection and exclusion processes

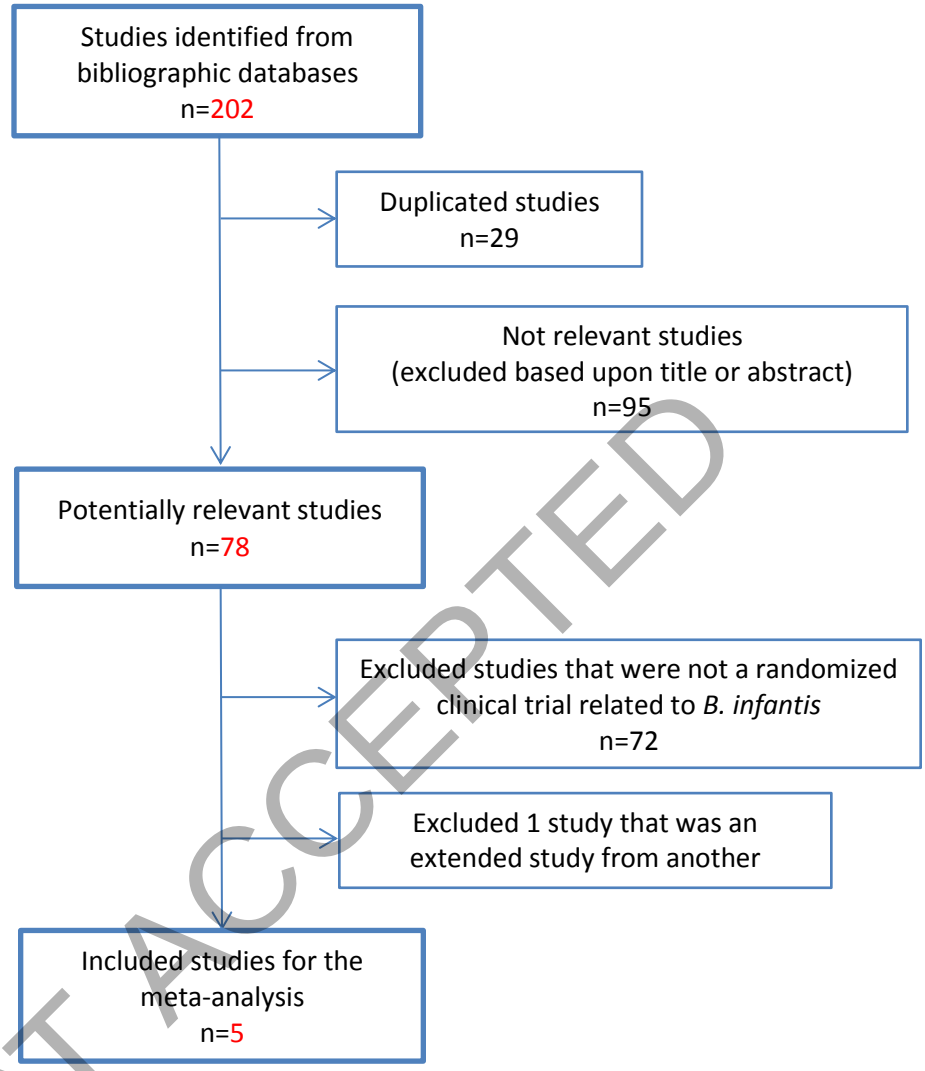
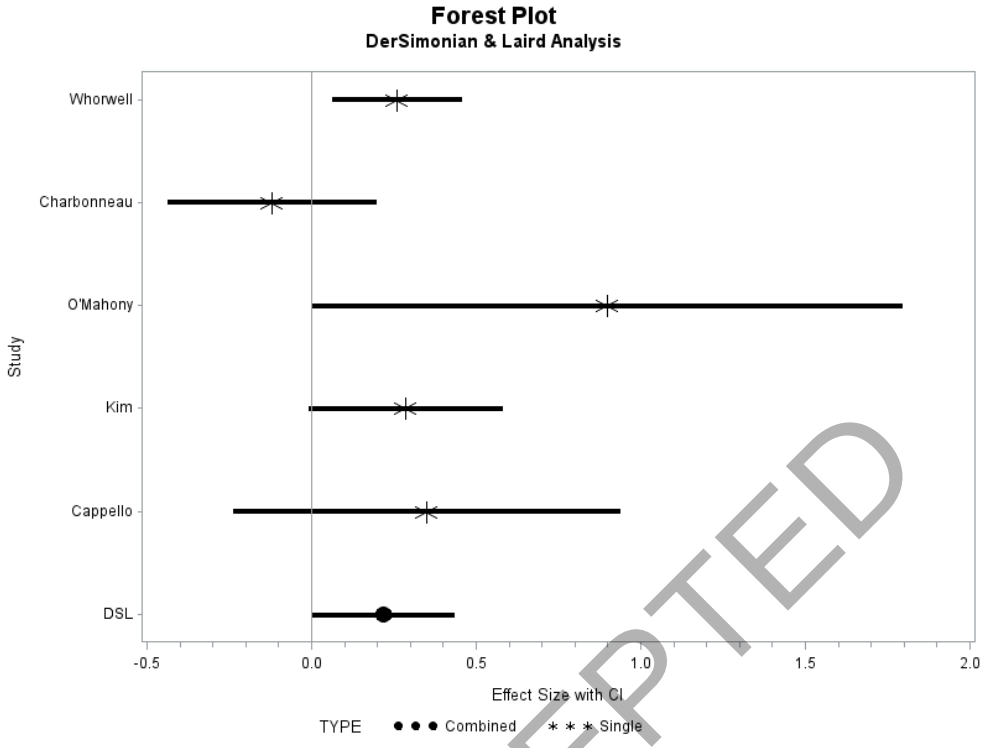
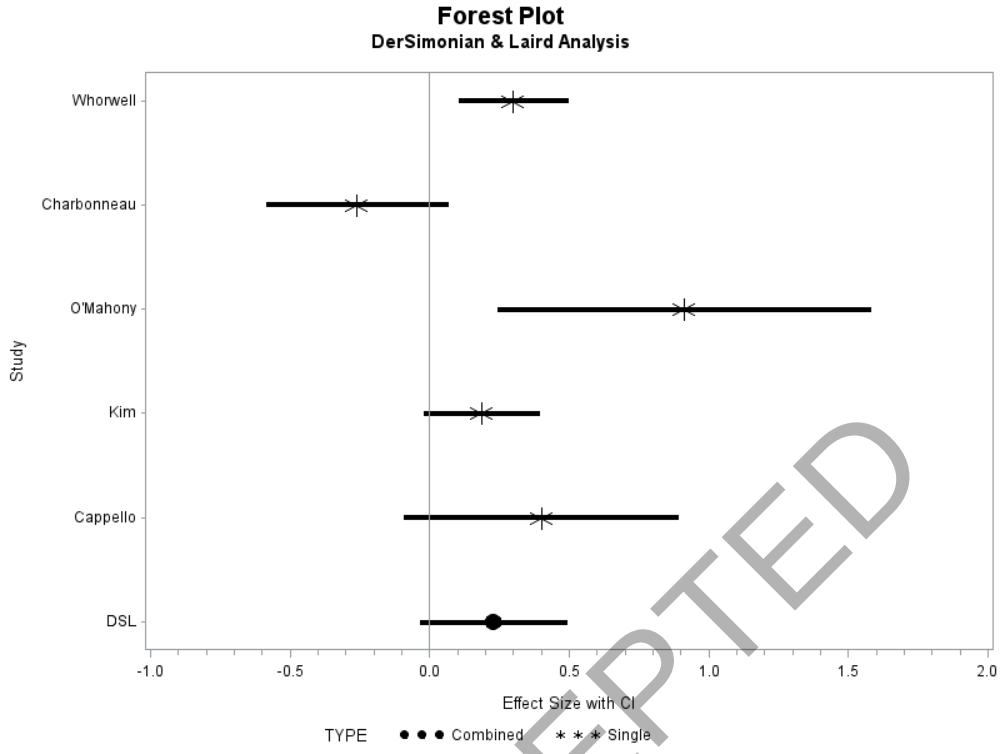


Figure 2. Forest plot for bloating/distention based on the five studies



*DSL (DerSimonian and Laird) stands for the combined effect based on the fixed-effect model (I-squared<50%).

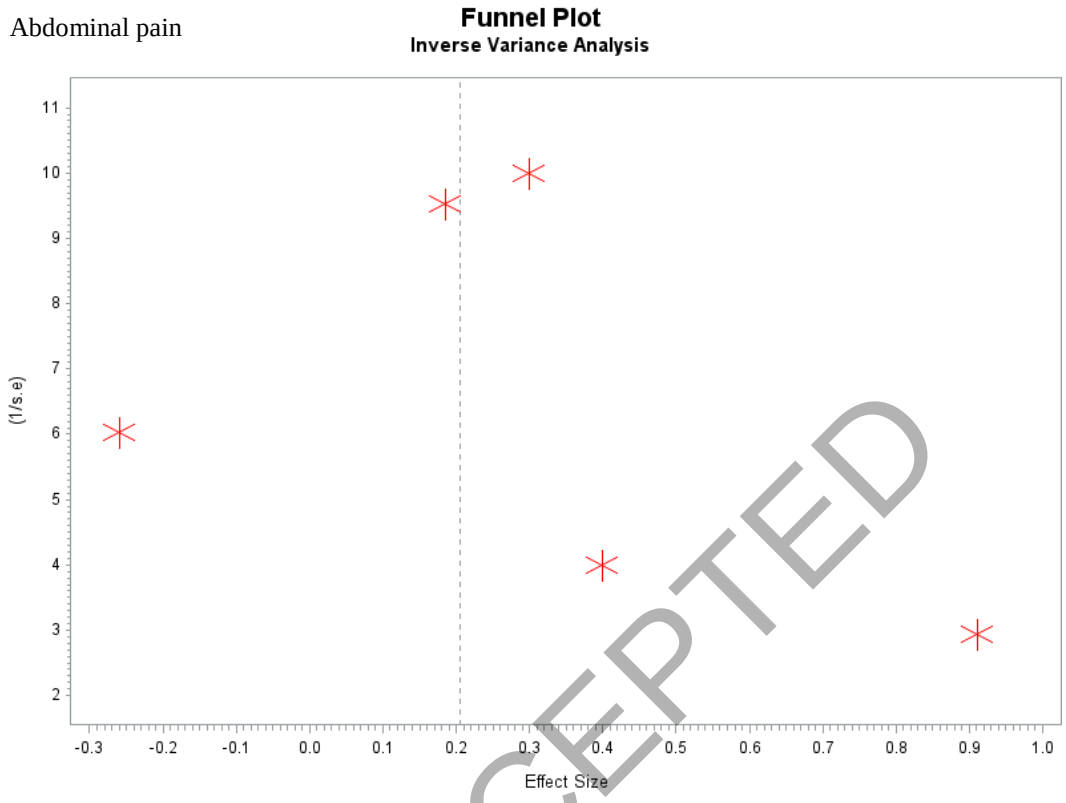
Figure 3. Forest plot for abdominal pain based on the five studies



*DSL (DerSimonian and Laird) stands for the combined effect based on the random-effect model (I-squared>50%).

Figure 4. Funnel plots for abdominal pain and bloating/distention based on the five studies

a) Abdominal pain



b) Bloating/distention

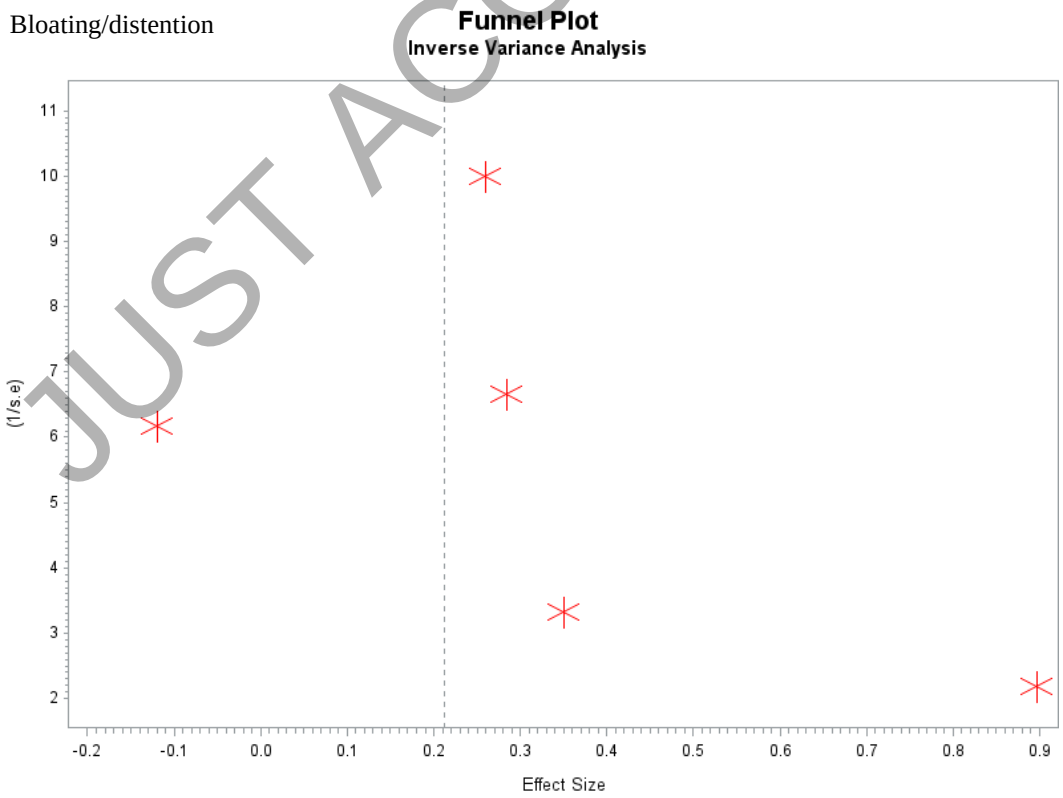


Table 1. Characteristics of the studies included in the systematic review

Study	Study design	Completeness of ITT	Sample	Mean age (years)	Sex (Female)	Subtype	Study drug	Jadad Scale
Whorwell, et al. (2006)	Multicenter DBPCT	100%	362	41.9	100%	55.5% D-IBS; 20.7% C-IBS; 23.8% M-IBS	***B. infantis 35624***; placebo	4
Charbonneau, et al. (2013)	Single-center DBPCT	83%	117	45.5	81%	Include D-IBS, C-IBS and M-IBS.	***B. infantis 35624***; placebo	4
O'Mahony, et al. (2005)	Single-center DBPCT	100%	75	44.3	64%	28% D-IBS; 26% C-IBS; 45% M-IBS	***B. infantis 35624***; L.salivarius ucc4331	5
Kim, et al. (2005)	Single-center DBPCT	100%	48	40 vs 46	94%	Not reported	VSL# 3 of composite probiotic: Bifidobacterium (B. longum, ***B. infantis*** and B. breve), Lactobacillus (L. acidophilus, L. casei, L. delbrueckii ssp. bulgaricus and L. plantarum), and Streptococcus salivarius ssp. thermophilus; placebo	5
Cappello, et al. (2013)	Single-center DBPCT	94%	64	36.6 vs 40.8	64%	36% D-IBS; 39% C-IBS; 22% M-IBS; 3% undetermined	Symbiotic mixture contains lyophilizxed bacteria (L. plantarum, L. casei, L. gasseri, ***B. infantis***, B. longum, L. acidophilus, L. salivarius, L. sporogenes, S. thermophilus) and as prebiotic Inulin and Tapioca-resistan starch; placebo	5

ITT, intention-to-treat; DBPCT, double–blind placebo controlled test; D-IBS, Diarrhea-Irritable Bowel Syndrome; C-IBS, Constipation - Irritable Bowel Syndrome; M-IBS, Mixed-Irritable Bowel Syndrome.

Table 2. The primary outcomes of clinical symptom and sign in patients treated with *B. Infantis* and placebo

Studies	Duration	Abdominal pain				Bloating/distention				Bowel habit satisfaction			
		B. Infantis		Placebo		*B. Infantis*		Placebo		*B. Infantis*		Placebo	
		Mean	SE [a]	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
1) Whorwell, et al.	4 weeks	1.43	0.10	1.73	0.10	1.70	0.10	1.96	0.10	1.92	0.09	2.21	0.09
2) Charbonneau, et al.	8 weeks	1.99	0.16	1.73	0.17	2.01	0.16	1.89	0.17	1.77	0.17	1.65	0.18
3) O'Mahony, et al.	8 weeks	1.58	0.28	2.49	0.40	1.94	0.39	2.84	0.52	1.86	0.36	4.08	0.47
4) Kim, et al.	4 weeks	1.19	0.11	1.37	0.11	1.62	0.15	1.91	0.15	Not applicable			
5) Cappello, et al.	4 weeks	1.25	0.25	1.65	0.25	1.35	0.30	1.70	0.30	Not applicable			
Estimated difference and SE based on the studies 1-3 (*B. Infantis* only)		0.25 (0.26) [b]				0.20 (0.20) [b]				0.66 (0.39) [b]			
95% confidence interval		(-0.27, 0.77)				(-0.19, 0.58)				(-0.11, 1.43)			
Estimated difference and SE based on the studies 4-5 (composite probiotic)		**0.22 (0.10) [c]**				**0.30 (0.13) [c]**							
95% confidence interval		**(0.03, 0.41)**				**(0.04, 0.56)**							
Estimated difference and SE based on the studies 1-5		0.23 (0.13) [b]				**0.21 (0.07) [c]**							
95% confidence interval		(-0.03, 0.49)				**(0.07, 0.35)**							

[a]SE stands for standard error.
[b]Random model was used because of notable heterogeneity (I-squared ≥50%).
[c]Fixed model was used because of only mild heterogeneity (I-squared <50%).