World Journal of Pediatrics (2022) 18:320–332
https://doi.org/10.1007/s12519-022-00516-6

META-ANALYSIS

Effects of probiotic supplementation on abdominal pain severity in pediatric patients with irritable bowel syndrome: a systematic review and meta-analysis of randomized clinical trials

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Received: 26 August 2021 / Accepted: 3 January 2022 / Published online: 1 February 2022

Abstract

Background Probiotic supplementation has been used to alleviate abdominal pain in children and adolescents with irritable bowel syndrome (IBS), but the evidence is not compelling. Thus, a systematic review and meta-analysis of randomized clinical trials (RCTs) were performed to investigate the effects of probiotic supplementation on abdominal pain in pediatric patients with IBS.

Methods PubMed/MEDLINE, Web of Science, Scopus, Cochrane Library, and Embase were the available databases searched to find relevant randomized clinical trials up to April 2021. The effect size was expressed as weighted mean difference (WMD) and 95% confidence interval (CI).

Results Seven RCTs with 441 participants were included, from which the meta-analysis demonstrated that probiotic supplementation has a significant effect on reducing abdominal pain in pediatric patients with IBS (WMD = − 2.36; 95% CI − 4.12 to − 0.60; $P = 0.009$). Although our study involved children and adolescents (≤ 18 years), the effects of probiotic supplementation seem to be more potent in patients under 10 years old (WMD = − 2.55; 95% CI − 2.84 to − 2.27) compared to patients aged 10–18 years (WMD = − 1.70; 95% CI − 2.18 to − 1.22). The length of supplementation longer than four weeks was more effective (WMD = − 2.43; 95% CI − 2.76 to − 2.09).

Conclusion Probiotic supplementation can reduce abdominal pain in pediatric patients with IBS.

Keywords Abdominal pain · Adolescents · Irritable bowel syndrome · Meta-analysis · Probiotic

Introduction

Irritable bowel syndrome (IBS) can be considered a multifactorial disease that markedly affects the patients' welfare [1]. Its symptoms are chronic and predominantly characterized by abdominal pain and altered bowel habits [2]. The pathophysiology and diagnosis of IBS have been widely discussed among the scientific community [3].

IBS is linked to a cluster of inflammatory, immune, and neuroendocrine mechanisms which contribute to visceral hypersensitivity and chronic inflammation of the small intestine and colon, as well as increased intestinal permeability [4]. In addition, the gut-brain axis is a target to be modulated in IBS mainly in virtue of neurotransmitter levels [5]. So much so that pain modulation, gastrointestinal dysmotility, and alteration in neurotransmitters and their receptors appear to play a pivotal role in the development of IBS [6, 7]. Not surprisingly, a scientific effort is still exercised to elucidate

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these mechanisms; for instance, the crosstalk between the gut microbiota and enteroendocrine and enterochromaffin cells, known as neuropods, has gained attention in understating visceral pain by yielding synaptic-like connections with local neural fibers and hence stimulating neurotransmission between the epithelial layer and the nervous system [8, 9].

The Rome IV criteria are frequently used for the clinical diagnosis of IBS, involving recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with two or more of the following items: (1) related to defecation; (2) associated with a change in frequency of stool; and (3) associated with a change in the appearance/form of stools [10]. The global burden of abdominal pain remains a challenge in the management of children's welfare, mainly those diagnosed with IBS [11]. It is no wonder that epidemiological studies consider IBS as one of the main gastrointestinal disorders among the pediatric population, which vary according to predisposing factors (e.g., bacterial overgrowth and food-related problems) [12–16]. More specifically, prevalence rates of IBS among children and adolescents range between 3 and 12% worldwide, with a higher prevalence between 8 and 12 years [5, 17].

While there is robust evidence supporting probiotics for improving overall symptoms in adults with IBS, as confirmed by a network meta-analysis [18], emerging research has considered probiotic supplementation as a promising and feasible candidate to alleviate general gastrointestinal symptoms and abdominal pain in children and adolescents with IBS [19]. In this population, great interest has been directed towards abdominal pain, as shown by a couple of randomized clinical trials (RCTs) [20, 21]. In an attempt to draw firm conclusions for the circles of clinical practice, therefore, we carried out a systematic review and meta-analysis of RCTs to investigate the overall effects of probiotic supplementation in reducing abdominal pain in pediatric patients with IBS.

Methods

The Preferred Reporting Items for Systematic Review and Meta-analysis statement criteria was applied for performing the current study [22]. Also, the study protocol was ethically approved by the Regional Bioethics Committee of Shahid Beheshti University of Medical Sciences.

Search strategy

A systematic search was implemented in the Scopus, Embase, PubMed, Web of Science, and Cochrane library databases from inception until April 2021. The combination of the following keywords and Medical Subject Heading (MeSH) terms were used in the search strategies: (probiotics OR lactobacillus OR bifidobacterium) AND (irritable bowel syndrome OR IBS) AND (child OR adolescent OR pediatrics). We also hand-searched the bibliographies of retrieved reviews to find further potentially relevant papers. No language or time limits were imposed in the literature search.

Eligibility criteria

After the elimination of duplicate records, titles and abstracts of identified papers were screened in detail, and studies with the following criteria were included: (1) randomized controlled trial design; (2) use of probiotics supplementation as an intervention; (3) enrolling children and adolescents (under or equal to 18 years of age) with IBS; and (4) reporting sufficient data on the severity of abdominal pain score. Studies without control groups, non-randomized trials, and studies conducted on pregnant women or adults were excluded. We also excluded studies that did not provide sufficient data on intended outcomes as well as those enrolled healthy subjects.

Data extraction

A detailed full-text review was independently performed by two authors and the following data were abstracted using standardized pre-piloted forms: first author's name, year of publication, study location, sample size, RCT design, type of probiotic supplement dose and duration of intervention, participants' characteristics (gender, mean age, mean body mass index), and the means and standard deviations (SDs) of outcome measures in both intervention and control groups.

Quality assessment

The methodological quality assessment of eligible RCTs was done in accordance with the Cochrane risk of bias criteria [23]. Studies were subjectively rated by two authors as high, low, or unclear risk of bias based on the following domains: allocation concealment, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, random sequence generation, selective reporting, and other bias. Any disagreements were resolved by a third reviewer.

Data synthesis and statistical analysis

Data were analyzed using comprehensive meta-analysis version 2.0 and STATA version 12.0 software and results were expressed as weighted mean differences (WMDs) with a 95% confidence interval (CI). In the absence of SD of the change, we computed it using the following formula: SD change = square root [(SD baseline 2 + SD final 2) − (2 × R × SD baseline × SD final)] [24, 25]. Also,

for trials that only reported standard error of the mean (SEM), SDs were computed using the following formula: $SD = SEM \times \sqrt{n}$, where "n" is the number of subjects in each group. The differences in means and SDs were computed to estimate the overall effect size under the random-effects model [24, 26]. Inter-study heterogeneity was assessed using Cochrane Q statistic and quantified by I^2 statistic [27]. To explore the potential sources of heterogeneity, we conducted subgroup analysis based on the mean age of participants (< 10 years or ≥ 10 years) and duration of the intervention (≤ 4 weeks or > 4 weeks) [28]. The sensitivity analysis was carried out to assess the robustness of findings by the leave-one-out method. Moreover, we examined the presence of publication bias using visual inspection of funnel plot and Egger's regression test [29].

Results

Study selection

The process of extraction and exclusions is shown in Fig. 1. After searching the systematic databases, 1873 articles were selected, with 1235 articles being remained after the elimination of duplicate studies. Then, 1212 articles were deleted after reviewing the abstract or title according to the inclusion criteria, and 16 articles were discarded after retrieving the full text of the remaining 23 articles. Finally, seven articles met the eligibility and were included in our analysis [21, 30–35].

Study characteristics

The general characteristics of the eligible studies are summarized in Table 1, confirming that children and adolescents with IBS were the populations examined, in which the highest mean age among the studies was 12.5 years. Our meta-analysis demonstrated that probiotic supplementation has a significant effect on reducing abdominal pain in children and adolescents with IBS. Although our study involved children and adolescents up to 18 years old, the effects of probiotic supplementation seem to be most potent in patients younger than 10 years.

Studies were published between 2006 and 2020; two studies were conducted in Italy and other studies were performed in Poland, Iran, the USA, and India. The mean age and sample size of studies' participants varied between 6.5 and 12.5 years and 37–132, respectively, with the duration

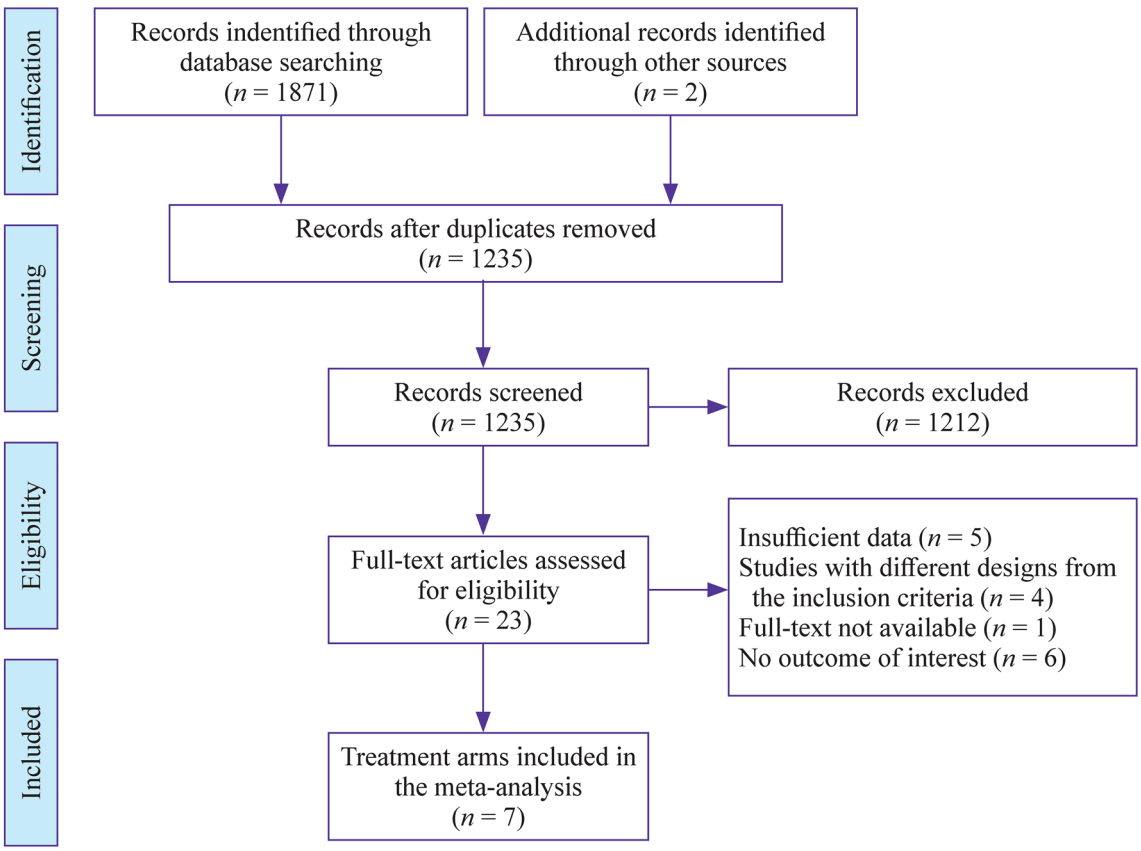

Fig. 1 Flowchart of the selected studies, including identification, screening, eligibility and the final sample included

of intervention ranging from 4 to 8 weeks. In four studies, *Lactobacillus rhamnosus* GG probiotic was used as the intervention group and in one study 108 colony forming units *Lactobacillus reuteri* was evaluated. In other studies, probiotics VSL#3 and *Bacillus coagulans* Unique IS2 were used in the intervention group. Also, the faces pain scale, Likert scale, irritable bowel severity scoring system, subject's global assessment of relief questionnaires and Wang-Baker faces pain rating scale were used to assess the severity of abdominal pain.

Risk of bias assessment

The details of the study quality assessment are presented in Supplementary Table 1. As shown in the table, six studies were rated with low risk in random sequence generation, because they did not explicitly mention the random sequence generation methods and one as unclear risk. All studies were rated as unclear risk in allocation concealment. Four study reported that both the participants and the researchers were blinded and was, thus, identified as having a low risk of bias for the blinding step. Five of the trials provided a clear description of the blinding of outcome assessment. Seven studies were clear on providing incomplete outcome data and then were considered as low risk of bias. Four studies were assessed as having a low risk of bias in selective reporting, and the other article were rated as unclear risk of bias. Except for one study that was considered as high risk of bias in the quality stage, the other studies were considered as unclear risk of bias.

Meta-analysis

Effect of probiotics supplementation on the severity of abdominal pain

The quantitative meta-analysis revealed a significant effect of probiotic supplementation on the severity of abdominal pain score (WMD = − 2.36; 95% CI − 4.12 to − 0.60; $P = 0.009$). However, a significant heterogeneity was observed among the studies for this outcome (Cochran Q test, $P < 0.001$, $I^2 = 99.9\%$) (Fig. 2). Stratified analysis, according to mean age of participants and duration of the intervention, indicated a significant change in the results for the severity of abdominal pain score. Probiotic supplementation in patients < 10 years old (WMD = − 2.55; 95% CI − 2.84 to − 2.27) compared to patients aged 10–18 years (WMD = − 1.70; 95% CI − 2.18 to − 1.22). The length of supplementation longer than four weeks was more effective (WMD = − 2.43; 95% CI − 2.76 to − 2.09) (Supplementary Figs. 1, 2). None of the subgroup analyzes for the age of the participants and the duration of the intervention could find a possible source of heterogeneity.

Sensitivity analysis

The leave-one-out method was applied to assess the influence of each study on the pooled effect size. The findings remained robust after the sequential elimination of studies (Supplementary Fig. 3).

Publication bias

Visual inspection of the funnel plot revealed no evidence of publication bias regarding the impacts of probiotics supplementation on outcome measures. Additionally, the results of Egger's regression test supported the absence of significant publication bias for the severity of abdominal pain ($P = 0.54$) (Supplementary Fig. 4).

Discussion

This systematic review and meta-analysis of RCTs demonstrate that probiotic supplementation has a significant effect on reducing abdominal pain in children and adolescents with IBS. Although our systematic review included children and adolescents of various age (studies' mean age ranging from 6.5 to 12.5 years), the effects of probiotic supplementation seem to be most potent for patients younger than 10 years. In addition, supplementation duration longer than four weeks was most effective (compared to ≤ 4 weeks), but it is important to note that the longest length of supplementation was 8 weeks.

Similar to our findings, another meta-analysis confirmed that probiotic supplementation for children with IBS reduces abdominal pain score, strengthening this potential by accompanying reduction in Global Assessment of Relief score and frequency of abdominal pain while increasing the rate of abdominal pain treatment success [36]. However, contrary to the above study, we also observed this relationship in different age groups and the length of treatment.

It is noteworthy that IBS is a multifactorial disease affected by epigenetics and environmental problems such as an unbalanced diet, psychological factors, and socioeconomic factors, and is associated with common childhood illnesses such as asthma and/or atopic diseases [5]. The current pharmacological arsenal for IBS consists of loperamide, lubiprostone, tricyclic antidepressants, selective serotonin receptor inhibitors, antispasmodics, rifaximin, pregabalin, gabapentin, clonidine, and octreotide [37]. Equally important, non-pharmacological strategies are other approaches to IBS, involving cognitive-behavioral therapy [38] as well as supplements and dietary changes [39].

Regarding dietary aspects, fermentable carbohydrates called fermentable oligo-, di- and monosaccharides, and polyols (FODMAPs), along with different proportions and

Table 1 Characteristics of the subjects

Authors	Year	Country	Sex	Study design	Mean age (y)	Result of study	Sample size	Dose of intervention	Type of probiotics supplement	Inclusion/exclusion criteria	Durations (wk)	Tools to assess the severity of abdominal pain
Gawrońska et al. [32]	2007	Poland	Boy/girl	RCT	11.9	Those in the *Lactobacillus rhamnosus* GG group were more likely to have treatment success than those in the placebo group and reduced frequency of pain ($P=0.02$), but not pain severity ($P=0.10$)	37	3×10^9 cfu/mL, twice daily	*Lactobacillus rhamnosus* GG	Potentially eligible subjects received a diary to record symptoms and the frequency of daily pain, drug use and any symptoms they considered important for 4 wk before study inclusion. Patients were considered for study inclusion, if they were 6–16 y and had an abdominal pain disorder (i.e., FD or IBS or FAP) according to the Rome II diagnostic criteria 3 valid at the time of the design of the study. To establish the diagnosis, the patients completed questionnaires covering baseline assessment, exclusion criteria and the Rome II diagnostic criteria. Exclusion criteria included organic disease (as established by medical history, complete blood count, urinalysis, stool examination for occult blood, ova and parasites, blood chemistries, abdominal ultrasound, breath hydrogen testing and endoscopy, if needed), other chronic disease and growth failure	4	Faces pain scale
Rahmani et al. [35]	2020	Iran	Boy/girl	RCT	7.5	Probiotic treatment (*Lactobacillus reuteri*) significantly improved the intensity and the duration of RAP. All pain-related characteristics, such as the frequency of days of pain, the severity of pain, the duration of pain, and its pattern in the case group, were significantly reduced upon the treatment in comparison with the control group	30	Unclear	Probiotic chewable tablets (containing 108 colony forming units *Lactobacillus reuteri*)	Children who were included in the study were between the ages of 6 and 16 y, and the diagnosis of nonorganic RAP was performed according to ROME III criteria. The following were excluded from the study: the presence of any one of the red flag items, use of antibiotics in the last 1 mon, organic disorder based on clinical and paraclinical findings, and participants or parents who did not co-operate in regards with medications and referrals	4	Wang-Baker faces pain rating scale

Table 1 (continued)

Authors	Year	Country	Sex	Study design	Mean age (y)	Result of study	Sample size	Dose of intervention	Type of probiotics supplement	Inclusion/exclusion criteria	Durations (wk)	Tools to assess the severity of abdominal pain
Kianifar et al. [21]	2015	Iran	Boy/girl	RCT	6.8	The severity of the patients' pain decreased significantly in the intervention group after 1, 2, 3, and 4 wk of treatment, as indicated by *P* values of 0.01, 0.00, 0.00, and 0.00, respectively. Also, there was significant improvement in the functional scale after 2 wk of treatment ($P \leq 0.00$)	52	1×10^{10} cfu/mL	*Lactobacillus rhamnosus* GG	The inclusion criteria were patients whose ages ranged from 4 to 18 y who had active symptoms of abdominal pain for at least 2 wk before the beginning of the study and had been diagnosed with IBS by a pediatric gastroenterologist. This diagnosis must have been made on the basis of Rome III criteria and other differential diagnoses must have been excluded by laboratory evaluation, abdominal ultrasound, radiographic imaging, endoscopy, and breath hydrogen testing, if needed. Patients were excluded if they were taking any drugs or had underlying diseases (cardiac disease, renal disease, asthma, failure to thrive, cystic fibrosis)	4	Five-point Likert scale
Bausserman et al. [34]	2005	USA	Boy/girl	RCT	11.6	*Lactobacillus rhamnosus* GG was notsuperior to placebo in relieving abdominal pain (40.0% response rate in the placebo group vs. 44.0% in the *Lactobacillus rhamnosus* GG group; $P = 0.774$). There was no difference in the other gastrointestinal symptoms, except for a lower incidence of perceived abdominal distention ($P = 0.02$ favoring *Lactobacillus rhamnosus* GG)	50	10^{10} twice daily	*Lactobacillus rhamnosus* GG	All children had a previous evaluation by a pediatric gastroenterologist, who made the diagnosis of IBS and excluded organic disease as a cause of abdominal pain. All children fulfilled Rome II criteria for IBS. Patients had active symptoms of abdominal pain over a period of at least 2 wk before initiating the study. Children were excluded if they were under age 5 y or over age 21 y, receiving medication for the treatment of IBS (including alternative medical therapy, such as herbal remedies or probiotics), receiving antibiotic therapy, or receiving drugs known to cause abdominal pain	6	Severity score based on 4-point Likert scale

Table 1 (continued)

Authors	Year	Country	Sex	Study design	Mean age (y)	Result of study	Sample size	Dose of intervention	Type of probiotics supplement	Inclusion/exclusion criteria	Durations (wk)	Tools to assess the severity of abdominal pain
Francavill et al. [33]	2010	Italy	Boy/girl	RCT	6.5	Compared with baseline, *Lactobacillus rhamnosus* GG, but not placebo, caused a significant reduction of both frequency ($P<0.01$) and severity ($P<0.01$) of abdominal pain	80	3×10^9, twice daily	*Lactobacillus rhamnosus* GG	Patients were recruited from 9 primary care pediatricians chosen from communities throughout the territory by random selection. Children (5–14 y) of either gender with a diagnosis of IBS or FAP, according to the Rome II diagnostic criteria, valid at the time of the design of the study, were considered eligible. The diagnosis of IBS or FAP was based on a clinical interview performed by the same physician. Children were excluded if they (1) had any chronic diseases, (2) received treatment with antibiotics/probiotics in the previous 2 mon, (3) had a pain history suggestive of functional dyspepsia/aerophagia/abdominal migraine, (4) exhibited growth failure, (5) had gastroparesis, (6) had gastrointestinal obstructions/stricture, (7) displayed alarming signs of organic conditions, (8) had previous abdominal surgery, or (9) had abnormal baseline test results (including complete blood counts; erythrocyte sedimentation rate; liver-pancreas-kidney function tests; tissue transglutaminase with immunoglobulin A measurement; stool examination for occult blood, ova, and parasites; fecal calprotectin; urinalysis; C-urea breath test; and abdominal ultrasound)	8	Severity score based on combination of the self-reported visual analog scale and the faces pain scale was used

Table 1 (continued)

Authors	Year	Country	Sex	Study design	Mean age (y)	Result of study	Sample size	Dose of intervention	Type of probiotics supplement	Inclusion/exclusion criteria	Durations (wk)	Tools to assess the severity of abdominal pain
Guandalini et al. [31]	2010	Italy	Boy/girl	RCT	12.5	Although placebo was effective in some of the parameters and in as many as half of the patients, VSL#3 was significantly superior to it ($P<0.05$) in the primary endpoint, the subjective assessment of relief of symptoms; as well as in 3 of 4 secondary endpoints: abdominal pain/discomfort ($P<0.05$), abdominal bloating/gassiness ($P<0.05$), and family assessment of life disruption ($P<0.01$)	60	1 sachet of VSL#3 (once per day for children 4–11 y; twice per day for those 12–18 y)	VSL#3 probiotic mixture	Exclusion criteria were any chronic organic gastrointestinal disorders, as assessed by full clinical history and examination, and supported by normal results of initial limited laboratory investigation including complete blood cell count with differential, erythrocyte sedimentation rate, C-reactive protein, amylase and lipase, tissue transglutaminase antibodies with total serum IgA, and fecal occult blood. All of the above tests were performed in every patient; additionally, fecal calprotectin was checked in some cases at the physician's discretion. Any abnormality in any of the tests resulted in the patient's exclusion from the study. Also excluded were patients presenting any disease that may affect bowel motility such as diabetes mellitus, sarcoidosis, connective tissue disease, or poorly controlled hypo-/hyperthyroidism. Additional exclusion criteria were previous abdominal surgery, as well as significant concomitant psychiatric, neurological, metabolic, renal, hepatic, infectious, hematological, cardiovascular, or pulmonary illnesses. Finally, patients who had been using any commercial preparation of probiotics during the previous 3 mon were likewise excluded	6	Subject's global assessment of relief

Table 1 (continued)

Authors	Year	Country	Sex	Study design	Mean age (y)	Result of study	Sample size	Dose of intervention	Type of probiotics supplement	Inclusion/exclusion criteria	Durations (wk)	Tools to assess the severity of abdominal pain
Sudha et al. [30]	2018	India	Boy/girl	RCT	7.9	*Bacillus coagulans* Unique IS2 treated group showed a greater reduction in pain scores as evaluated by a weekly pain intensity scale. There was a significant reduction ($P<0.0001$) in pain intensity in the probiotic treated group (7.6 ± 0.98) as compared to the placebo group (4.2 ± 1.41) by the end of the treatment period (8 wk)	132	2×10^9 cfu	*Bacillus coagulans* Unique IS2	Inclusion criteria were patients of either sex between 4 and 12 y. All enrolled patients were diagnosed with IBS as defined by Rome III criteria. Patients having any of the following symptoms were included in the study: abnormal stool frequency defined as greater than 3 bowel movements per day or less than 3 bowel movements per week; abnormal stool form (lumpy/hard or loose/watery); abnormal stool passage (straining, urgency or feeling of incomplete evacuation); passage of mucus with stool and bloating or abdominal distension. Exclusion criteria included patients diagnosed with other diseases affecting bowel motility other than IBS. Those with a history of lactose intolerance and other malabsorption syndromes (e.g., fructose malabsorption), previous abdominal surgery and patients suffering from severe systemic disease were also excluded. Other exclusion criteria included those who had been using commercial preparation of probiotics in the last 3 mon, history of digestive disease (Crohn's, ulcerative colitis, oesophagitis, peptic ulcer, coeliac disease) or symptoms suggestive of rectal bleeding, and weight loss over 3 kg in the last 3 mon as well as acute gastroenteritis in the last 4 wk prior to inclusion	8	Subject's global assessment of relief

RCT randomized clinical trial, *FD* functional dyspepsia, *IBS* irritable bowel syndrome, *FAP* functional abdominal pain, *RAP* recurrent abdominal pain, *IgA* immunoglobulin A

types of proteins and fats, as well as the intake of coffee and hot spices, are generally linked to abdominal pain [40]. These foodstuffs can imply gastrointestinal problems even in healthy people, while further intensifying the bowel motility and abdominal distention in patients with IBS who naturally have visceral hypersensitivity [40]. Nevertheless, given that decreasing FODMAPs, especially in childhood, can induce nutrient restriction, our meta-analysis examined interventions based only on probiotics to generate results with greater clinical adhesion, as probiotic supplements are administrated via capsules or sachets while dietary interventions are more susceptible to biases due to different habits and incorrect eating choices. Furthermore, despite the pharmacological efficacy in IBS [41], the investigation of probiotic supplements in our study is relevant to provide the magnitude of an adjuvant therapy or even a major strategy in the management of children and adolescents since two or more concurrent medications may be considered pediatric polypharmacy and it is often difficult to administer medicines for children [42], whereas probiotics have no residual flavor and can be easily diluted in liquids. Indeed, it is essential to investigate in scrutiny the types of probiotic supplements in pediatric digestive disorders, as the gut microbiota modulation cannot be neglected in children and adolescents with IBS [43]. So much so that dysbiosis is associated with increased abdominal pain in this population, whereby an unhealthy gut microbiota leads to growth in pathogenic bacteria and a decrease in commensal bacteria [44]. Before considering the supplementation of probiotics as a means of mitigating these harmful effects, it is worth mentioning the bacteria species present in the pathophysiology of IBS so that a clinical rationale can be done.

Saulnier et al. observed that children with IBS had higher proportions of the phylum *Proteobacteria* (the class *γ-Proteobacteria*), genera such as *Dorea* (member of *Firmicutes*), *Haemophilus* (member of *γ-Proteobacteria*), as well as *Haemophilus parainfluenzae* and a novel *Ruminococcus*-like organism, while a greater status of the genus *Eubacterium* and the species *Bacteroides vulgatus* were noted in healthy children [45]. In addition, decreased bacterial diversity in the gut, such as some species like *Bifidobacterium*, *Collinsella*, and *Clostridiales* can also be detected in IBS [46]. Such a disturbance in the gut microbiota of patients with IBS may be related to impaired signal transduction pathways, with ensuing inflammatory state in the intestinal mucosa caused by Th17-related pro-inflammatory cytokines [e.g., interleukin (IL)-17A, IL-17F, and IL-22] [47–49]. History of previous gastrointestinal infections (e.g., infection by *Giardia lamblia*, *Salmonella* species, and *Campylobacter* species) seem to be involved in the etiology of IBS as well [19].

Regarding mechanisms, probiotics can enhance gut barrier function, inhibit pathogen binding, and modulate gut inflammatory response [50]. More specifically, as abdominal pain in IBS is related to elevated pro-inflammatory cytokine levels such as tumor necrosis factor-alpha, IL-1β, IL-6, and IL-12, increased intestinal mucosal permeability, and imbalance between commensal and pathogenic bacteria [44], probiotics could mitigate abdominal pain by restoring the gut microbiota and hence stabilizing colonic fermentation, whose actions physiologically decrease the inflammatory response and strengthen the intestinal mucosal barrier [41].

The studies selected in our meta-analysis ought to be individually discussed in view of providing particular attention to the types of probiotics used. *Lactobacillus rhamnosus* GG was the strain more used among the studies [21, 32–34]. For instance, Francavilla et al., working on 141 children with IBS, found that those who underwent *L. rhamnosus* GG had decreased frequency and intensity of abdominal pain compared to placebo, whose length of duration was 8 weeks [33]. The authors suggested that the improvement in symptomatology is secondary to an enhanced gut barrier [33]. Gawrońska et al. tested the effects of *L. rhamnosus* GG supplementation in children with IBS, functional dyspepsia, or functional abdominal pain ($n = 104$), observing moderate amelioration in abdominal pain symptoms for those who received the supplement [32]. Sudha et al. showed benefits in supplementing *B. coagulans* Unique IS2 for children with IBS, showing a decline in pain intensity, abdominal discomfort, bloating, staining, urgency, incomplete evacuation, and passage of gas, as well as improved stool consistency when compared to placebo [30]. This bacterial strain is used for many adult conditions [51, 52], and Sudha et al. [30] help in expanding the evidence for treating children.

Interestingly, however, not only isolated bacterial strain but also some studies examined the effects of commercial probiotic mixture. Guandalini et al. evaluated the efficacy of VSL#3 supplementation in children with IBS compared to placebo for 6 weeks, and those who supplemented with VSL#3 reported decreased abdominal pain, as well as improved abdominal bloating, gas, and subjective assessment of symptoms [31]. VSL#3 is a commercial probiotic mixture consisting of eight bacterial strains: four strains of *Lactobacillus* (*Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, and *Lactobacillus delbrueckii* subspecies *bulgaricus*), three strains of *Bifidobacterium* (*Bifidobacterium breve, Bifidobacterium longum*, and *Bifidobacterium infantis*), and one strain of *Streptococcus* (*Streptococcus salivarius* subspecies *thermophilus*) [53]. Collectively, synergic mechanisms are conceivable among these bacterial strains whereby the gene clusters of *Bifidobacterium* may enhance the intestinal barrier integrity by coding tight adherence pili, while several surface layer proteins of Lactobacilli display essential roles in the modulation of the host immune response by acting on the adhesion to host epithelium and extracellular matrix components

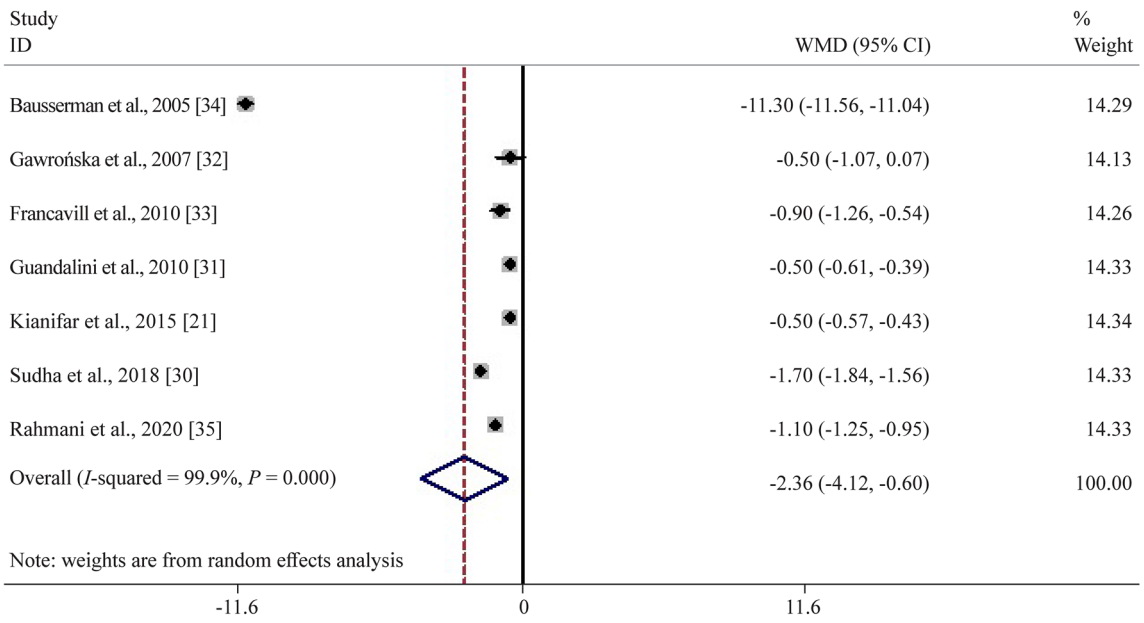

Fig. 2 Forest plot from the meta-analysis of clinical trials investigating the effects of probiotics supplementation on the severity of abdominal pain. *WMD* weighted mean difference, *CI* confidence interval

[53–55]. In addition, the gene clusters of *Streptococcus thermophiles* have abilities in coding most of the defense systems [53].

Our meta-analysis has strengths and limitations. This work brings practical data and enlarges the evidence geared toward the management of children and adolescents, whose is a population that can suffer from IBS and cannot be ignored. Along these lines, this research may assist the practice of general practitioners, pediatricians, and dietitians who deal with the pediatric population.

Moreover, in addition to improving the well-being of IBS patients, commercial probiotic supplements are apparently safe in general [56]; however, caution should be exercised to critically sick infants and patients with immune-compromised complexity due to the association between bacteremia and fungemia with some probiotic strains used as supplements, such as *Lactobacillus species* (mainly *L. rhamnosus*) and *Saccharomyces boulardii* [57]. As for limitations, the small number of high-quality RCTs on probiotics for IBS in various pediatric populations and the limited numbers of subjects recruited into many trials are the main limitations. Besides, due to insufficient study to obtain sufficient results, it was not possible to refer to other aspects IBS severity, e.g., stool ethnicity and frequency or any division based on subtype of IBS, as well as to perform subanalyses for probiotic strains.

In conclusion, this meta-analysis supports the favorable benefits of probiotic supplementation as a means of reducing the severity of abdominal pain in children and adolescents with IBS. However, a dose–response effect cannot be established so far, as the bacterial strain, dose, and duration of treatment vary substantially between studies. Therefore, further research is warranted, while practitioners (e.g., physicians and registered dietitians) should consider personalized dosing regimens based on their experience and the cost-effectiveness of the available products for current advice.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12519-022-00516-6.

Author contributions FS and HA contributed equally to this study. FS carried out the concept, design and drafting of this study, and performed the acquisition, analysis, and interpretation of data. SMH carried out the concept, design and drafting of this study, searched databases, screened articles and extracted data, and critically revised the manuscript. SA and SIGO performed the acquisition, analysis, and interpretation of data. SHO searched databases, screened articles and extracted data. All authors approved the final version of the manuscript.

Funding None.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval Ethical approval for this research was waived by its nature.

Conflict of interest None of the authors had any personal or financial conflicts of interest.

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